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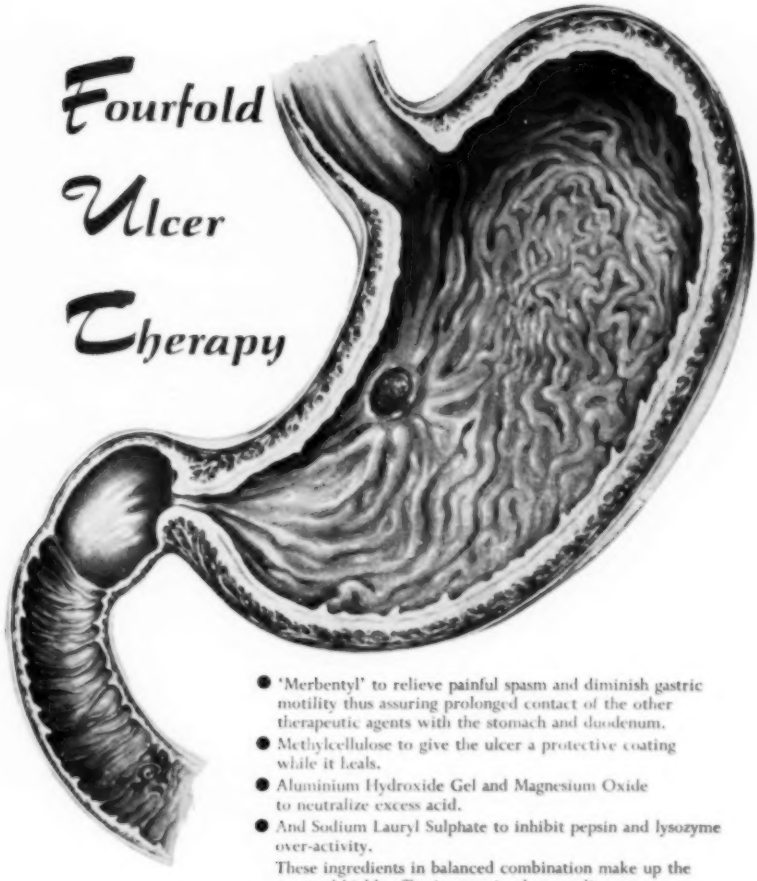

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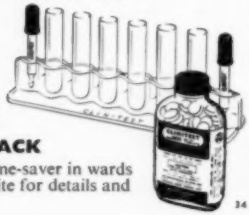

CLINITEST HOSPITAL PACK

An invaluable time-saver in wards and clinics. Write for details and hospital prices.

34

The advantages of ACETEST Reagent Tablets

Quick and reliable, a single tablet provides all the reagents to perform a test. Low cost permits this tablet test to be used as a screening procedure or as a routine for diabetic patients. No danger of false positives with normal urine No caustic reagents.

TO PERFORM A TEST:

1. **Put 1 drop of urine on tablet.**
2. **Take reading at 30 seconds. Compare tablet to colour chart provided.**
3. **Record results as negative, trace, moderate or strongly positive.**

Supplied in bottles of 100 tablets with colour scale.

'Acetest' Reagent Tablets *(diagnostic nitroprusside tabs.)* are also available under the N.H.S. on Form E.C.10. Basic Drug Tariff price 3/10 per bottle of 100 tablets (with colour scale).

REFERENCES

(1954) 'Clinical Tests for Ketonuria', *'Lancet' April 17th, pp.* 801/804

(1954) *'Medicine Illustrated', May, p.* 289

(1954) *'Practica Clinical Biochemistry', Heinemann, p.*74

(1954) 'Clinical Tests for Ketonuria', *'Lancet', July 10th, p.* 95

AMES COMPANY (LONDON) LTD.

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DON S. MOMAND LTD.

58 ALBANY STREET

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announcing

Achromycin*

HYDROCHLORIDE TETRACYCLINE HCl

Lederle

the true broad spectrum antibiotic

A new and outstandingly successful antibiotic—ACHROMYCIN Tetracycline—is now available for use in Great Britain and overseas countries. Developed by the Lederle research team, ACHROMYCIN is outstanding in many respects. Its stability and solubility surpass those of any broad-spectrum antibiotic in current use. Moreover, no case has yet been reported of the development of bacterial resistance to ACHROMYCIN. The antibacterial range of ACHROMYCIN is as great as that of any known antibiotic. Yet this new drug shows a remarkable freedom from undesirable side-effects. Prominent among the many indications for ACHROMYCIN are beta haemolytic streptococcal infections, *E. coli* infections, meningococcal, staphylococcal, pneumococcal and gonococcal infections ; acute bronchitis, bronchiolitis and certain mixed infections. Recommended basic adult dosage is 1 Gm. daily in divided doses—by mouth or injection.

- **More Rapid Absorption**
- **Fewer Side-Effects**
- **Greater Stability**

CAPSULES: 50 mg.—vials of 25 and 100. 250 mg.—vials of 16 and 100.

INTRAVENOUS: Vials of 250 mg. and 500 mg.

SPERSOIDS†: *Dispersible Powder:* Jars of 36 Gm. and 75 Gm. Each teaspoonful (3.0 Gm.) contains 50 mg. of Achromycin Tetracycline.

Other dosage forms are being developed as rapidly as research permits.

*Regd. Trade Mark †Trade Mark

Achromycin is at present only available for hospitals

LOOK TO Lederle FOR LEADERSHIP

LEDERLE LABORATORIES DIVISION

Cyanamid Products Ltd.

BUSH HOUSE, ALDWYCH, LONDON, W.C.2. TEMPLE BAR 5411

November 1, 1954
AUREOMYCIN*
CHLORTETRACYCLINE
Lederle
Can be prescribed on N.H.S. Form E.C.10
AUREOMYCIN means
GREATER ACTION
SMALLER DOSAGE
LOWER COST
*TRADE MARK
Technical literature on request
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As from Monday November 1, 1954, the restrictions imposed by the Ministry of Health, limiting the supply of AUREOMYCIN (Chlortetracycline) Hydrochloride Crystalline *Lederle* to hospitals, are completely removed. As from that date doctors are free to prescribe AUREOMYCIN in general practice whenever required for private or National Health Service patients without restrictions. AUREOMYCIN is manufactured in the United Kingdom and is in adequate supply for doctors and hospitals. AUREOMYCIN (Chlortetracycline) is the original broad-spectrum antibiotic which combines potency with safety and economy. More reports have appeared on the excellent clinical results with AUREOMYCIN than any other broad-spectrum antibiotic. There is a form of AUREOMYCIN for every purpose.

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Capsules
Dental Cones
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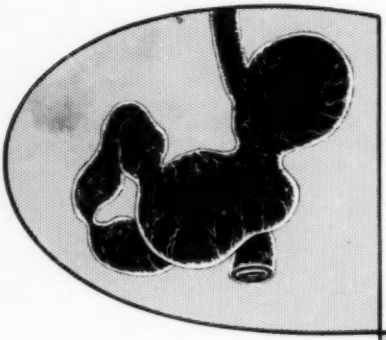
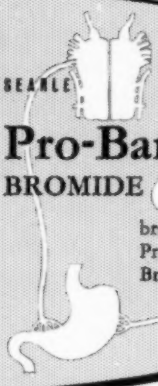


The potent anticholinergic agent for Gastric Hypermotility

The proven value of "Pro-Banthine" lies in its high potency as an anticholinergic agent, inhibiting transmission of neural stimuli at autonomic ganglia and parasympathetic myoneural junctions. By such inhibition "Pro-Banthine" reduces gastro-duodenal hypermotility, which is one of the causes of ulcer pain, and it is in striking confirmation of this that dosage with "Pro-Banthine" dramatically results in relief of pain.



"Pro-Banthine" is safe, easily administered and devoid of unpleasant taste. Pain relief and marked improvement is felt in most cases in 48 to 72 hours after starting "Pro-Banthine" treatment. Dosage is usually 15 to 30 mg. q.i.d. "Pro-Banthine" is supplied in 15 mg. tablets in bottles of 40, 100 and 1,000; and for parenteral use in 30 mg. vials in boxes of 6 and 25.

Literature on request.

*TRADE MARK.

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Ethical Pharmaceuticals since 1888

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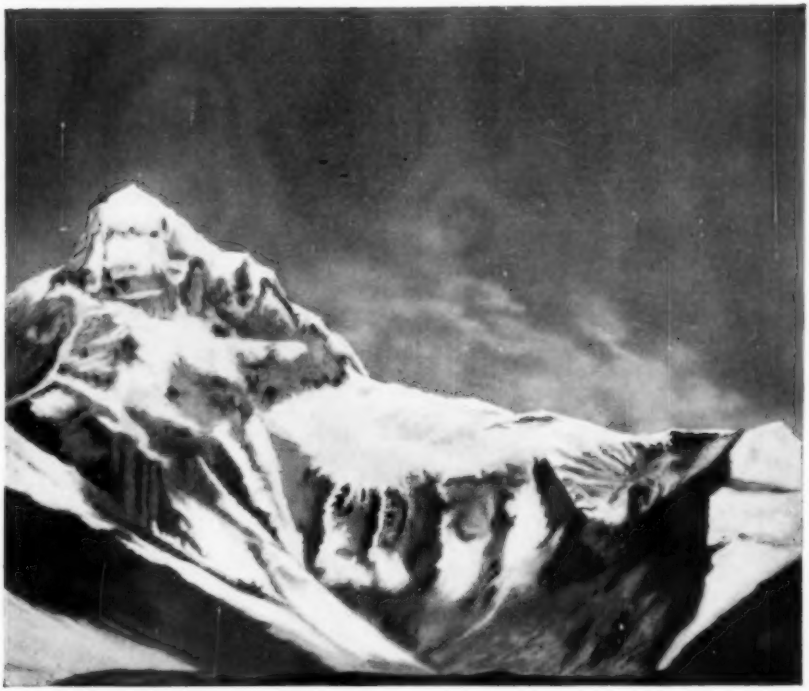


Highest peak concentrations and sustained therapeutic effect with 'ESKACILLIN'

the palatable liquid oral penicillin

Some authorities stress the value of high, if intermittent, peak penicillin serum concentrations; others favour lower, but sustained, plateau levels.

With 'Eskacillin' the advantages of both patterns are available. A very high peak concentration is achieved within about one hour of the first dose, succeeded by a more than adequate therapeutic level sustained for several hours.

'ESKACILLIN' 100 'ESKACILLIN' 200

'ESKACILLIN' 100 SULPHA

SMITH KLINE & FRENCH INTERNATIONAL CO.

represented by Menley & James, Limited, Coldharbour Lane, London, S.E.5

Tel: BRIxton 7851

ECP114

'Eskacillin' is a registered trade mark

applied with the vaginal applicator

confirmed in tolerability
aesthetically acceptable –
for simple, effective contraception

PRECEPTIN Vaginal Gel contains the active spermicidal agents
p-Diisobutylphenoxypolyethoxyethanol
and ricinoleic acid
in a synthetic base buffered at pH.4.5
LITERATURE ON REQUEST

Ortho Pharmaceutical Limited
HIGH WYCOMBE · BUCKINGHAMSHIRE · ENGLAND

Ortho

FERROMYN

(*Ferrous Succinate*)

A NEW ORGANIC IRON TABLET

the latest and most significant advance towards ideal oral iron therapy

FERROMYN is an original and logical approach to the problem of iron absorption and utilisation in the treatment of hypochromic anæmias and brings oral iron therapy a step nearer the ideal.

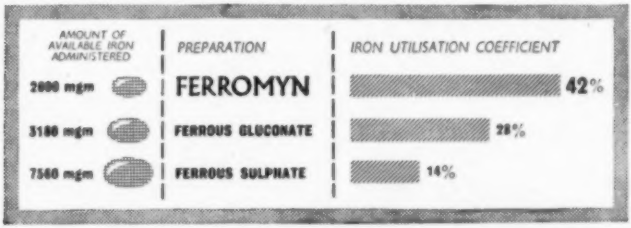
This new iron preparation presents Ferrous Succinate, a bivalent iron salt prepared from succinic acid, which, together with glycine is essential for the synthesis in the red bone marrow of a porphyrin (haem) containing iron.*

Normal Hb. and serum iron levels were demonstrated over an average period of 24 days treatment with a group of hypochromic anæmia patients with an average initial haemoglobin of 60%.

The controlled clinical trials with Ferromyn show an iron utilisation factor of 42% as compared with 14% Ferrous Sulphate and 28% Ferrous Gluconate.

This response was obtained with the low total average dosage of 2,604 mgm. available iron.

In comparison, the controlled group treated with Ferrous Sulphate required 42 days with an average dosage of 7,568 mgm. available iron to reach the same Hb. and serum-iron value.



FORMULA: *Each tablet contains 150 mgm. Ferrous Succinate, providing 35 mgm. elemental iron.*

PACKS AND PRICES: *Bottles of 100 tablets 4/2d plus P. Tax. Bottles of 1,000 tablets 38/8 plus P. Tax.*

***REF:** *The Lancet 14.3.53-p.533.*

FERROMYN

PRESCRIBE FERROMYN TABLETS BY NAME

CREWE
Telephone Crewe 3251-5

CALMIC LIMITED

LONDON
2 Mansfield Street, W.1
Telephone LANgham 8038-9

Let Sanatogen help you in treatment of

Stress Disorders

Hippocrates, in the fifth century B.C., taught that deductions are to be made only from observed facts. But only within the last hundred years has this basic principle borne fruit. Today the general practitioner treats many diseases with confidence and exact knowledge. But what of stress disorders?

EVIDENCE FOR SANATOGEN

Sanatogen has been successfully used as a nerve tonic for more than fifty years, with constantly increasing demand. Now that is a statement of observed fact which deserves consideration. We do not suggest that Sanatogen is the complete answer to stress disorders. Nevertheless, clinical evidence shows that the chemical combination contained in Sanatogen does produce remarkable results.

THE ROLE OF SANATOGEN

Sanatogen is 95% casein chemically combined with 5% sodium glycerophosphates. Three teaspoonfuls of Sanatogen t.d.s. (the normal dosage) provide the patient with 24 grams of protein daily, free from fat and cholesterol. Besides, its glycerophosphate content has a specific tonic effect on body and nerve tissue. Although Sanatogen is not prescribable owing to its high food value, it is being increasingly recommended by practitioners today because of the excellent results obtainable with this tonic. On the evidence, it is a fair deduction to say that Sanatogen is by far the best tonic available today for treatment of stress and strain.

Sanatogen

THE PROTEIN NERVE TONIC

The word 'Sanatogen' is a registered trade mark of Genatosan Ltd., Loughborough, Leics.

What can you do for my Rheumatism, Doctor?

What a difficult question this is to answer—particularly when put by an elderly patient. As an immediate resort, however, you can readily relieve the painful symptoms by prescribing Berex. Being a combination of salicylate and succinate, Berex enables a massive dosage of salicylate to be administered without lowering the prothrombin level, with less gastric disturbance and with the encouragement of tissue respiration.

SUMMARY OF FINDINGS OF A STUDY ON SUCCINATE-SALICYLATE THERAPY*

A succinate-salicylate combination has been found superior to acetylsalicylic acid in rheumatic states both on grounds of therapeutic efficacy and lower toxicity. Adequate amounts of the former could be administered with more lasting effect and with fewer and milder side effects. Furthermore, succinate-salicylate affects the disease process itself, as well as relieving painful symptoms and does not abnormally increase prothrombin time even after prolonged dosage.

**(January, 1954) Delaware State Medical Journal, 26, 22*

BEREX
Reg. Trade Mark

SUCCINATE-SALICYLATE THERAPY

for the relief of symptoms associated with all rheumatic disorders.

FORMULA:
Calcium Succinate 2.8 Gr.
Acetylsalicylic Acid 3.7 Gr.

★

A professional sample will be gladly sent on request.

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BEREX PHARMACEUTICAL CO.

MEDICAL DEPT: 110 JERMYN ST. S.W.1

. . . I've great faith in these Dalmas Tulle Gras Dressings

DALMAS TULLE GRAS DRESSINGS

SULPHONET

Wide mesh gauze impregnated with petroleum jelly, balsam of peru, and sulphathiazole 5%. A ready-to-use sterile dressing for wounds, burns, skin grafts and areas where there has been skin loss.
In squares 3¼" x 3¼" and strips 5 yds. x 3¼". Packed singly and in boxes of 5, 10 and 36 dressings. Available on E.C.10.

PETRONET (Paraffin Gauze Dressing, B.P.C.)

A sterile dressing impregnated with petroleum jelly and balsam of peru. For all lesions, abrasions, ulcers; these dressings ensure painless removal.
In squares 3¼" x 3¼" and packed singly and in boxes of dressings 5, 10 and 36. Also in strips of 8 yds. x 3¼". Available on E.C.10.

URO-SULPHONET

A strip dressing impregnated with a wool alcohol emulsion containing Sulphathiazole 5% and Urethane 2%. Provides a dressing that is bacteriostatic and analgesic; destroys offensive wound odour. Also an ideal burn dressing. Packed in a continuous strip 3¼" x 5 yds.

DALMAS

DALMAS LIMITED, LEICESTER & LONDON. Established 1823

Advances in antibiotics
with 'Penidural' Oral Suspension

THE NEW PENICILLIN COMPOUND
that remains stable for

2

YEARS WITHOUT REFRIGERATION

The discovery of a new penicillin salt .... DBED Dipenicillin G has resulted in the preparation of 'PENIDURAL' Oral Suspension. A stable fluid penicillin that retains its full potency in aqueous suspension for two years at normal room temperature *without refrigeration*, it is thus ideal for treatment in the patient's home.

'Penidural' is supplied ready for immediate use; THE PATIENT SIMPLY POURS THE SPECIFIED DOSE after shaking the bottle. The palatable aqueous syrup is readily accepted by children and adults, and provides substantial therapeutic blood levels in the systemic treatment of mild and moderately severe infections due to penicillin sensitive organisms.

300,000 units of Penicillin to each large teaspoonful (5 c.c.). Supplied in bottles of 60 c.c.

A substantial reduction in the price of 'Penidural' Oral Suspension has recently been made, due to improved methods of manufacture.

'PENIDURAL'

TRADE MARK

Benzathine Penicillin

Oral Suspension

Wyeth

JOHN WYETH & BROTHER LTD., CLIFTON HOUSE, EUSTON ROAD, LONDON, N.W.1

NOW *a New Form of an Effective Antibiotic*

Filmtab*

ERYTHROCIN REGD. Stearate

(ERYTHROMYCIN STEARATE, ABBOTT)

No more delayed action from enteric coating

Filmtab ERYTHROCIN Stearate tablets provide faster absorption, earlier blood levels. The new *Filmtab* (marketed only by Abbott) disintegrates far faster than enteric coatings—permits almost immediate drug absorption. Tests show ERYTHROCIN is adequately protected.

Result? The patient has high blood concentrations of ERYTHROCIN within 2 hours, instead of 4-6 hours as before. Peak level at 4 hours and significant concentrations for 8 hours.

ERYTHROCIN Stearate is highly effective—almost every gram-positive coccus is sensitive to its action. Especially recommended against staphylococci, because of the high incidence of staphylococcic resistance to penicillin.

ERYTHROCIN Stearate (compared with most other antibiotics) is less toxic—less likely to alter the normal intestinal flora. Gastro-intestinal disturbances are rare. No serious side effects reported.

Average adult dose is 200 mg. every four to six hours. *Filmtab* ERYTHROCIN Stearate tablets (100 mg. and 200 mg.) are available in bottles of 25 and 100. May we send you a sample of the new *Filmtab* ERYTHROCIN Stearate?

FOR LITTLE PATIENTS
Paediatric ERYTHROCIN Stearate Oral Suspension—Tasty, stable, ready-mixed.

* *(Trade Mark for Abbott's film-sealed tablets, patent applied for.)*

Prescribe ERYTHROCIN REGD. Stearate

(ERYTHROMYCIN STEARATE, ABBOTT)

ABBOTT LABORATORIES LTD • PERIVALE • GREENFORD • MIDDLESEX

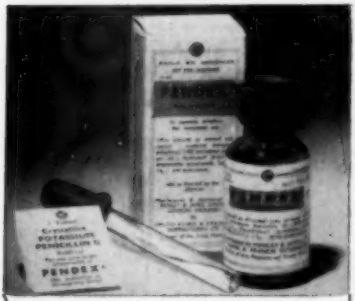
A range of nasal preparations to meet every need

'Paredrinex' Spraypak

liquid vasoconstrictor ½-fl. oz.

'Sulfex' nasal drops

sulphathiazole with vasoconstrictor
1-fl. oz. bottles, with dropper



'Pendex' nasal drops

penicillin with vasoconstrictor
15 ml. bottles, with dropper

'Benzedrine' Inhaler

volatile vasoconstrictor

For cost to N.H.S., please see M. & J. list of costs dated April, 1954

MENLEY & JAMES, LIMITED, COLDHARBOUR LANE, LONDON, S.E.5

for Smith Kline & French International Co., owner of the trade marks
'Paredrinex' 'Spraypak', 'Sulfex', 'Pendex', and 'Benzedrine'

NAP44

A BALANCED OUTLOOK

in anxiety states

Anxine Tablets provide the complete symptomatic treatment of anxiety states, psychoneuroses and psychosomatic disorders

by improving mood and increasing confidence,

by inducing gentle sedation and allaying anxiety and

by securing the optimal degree of muscular relaxation.

Although each of the three components of Anxine Tablets, dexamphetamine sulphate, cyclobarbitone and mephenesin, makes an important contribution to the amelioration of the symptoms of anxiety states, none is adequate alone. It is only when they are combined, in the form of Anxine Tablets, that synergism is achieved and the treatment is complete.

Formula

Each Anxine Tablet contains :

Dexamphetamine sulphate	2·5 mg.
Cyclobarbitone	35 mg.
Mephenesin	120 mg.

ANXINE

Available in bottles of 50 tablets

ALLEN & HANBURYS LTD · LONDON · E·2

TELEPHONE: BISHOPSGATE 8201 (12 LINES) TELEGRAMS: "CRYENBURYS, BETH, LONDON"

A new adjuvant in the treatment of respiratory disorders

Messrs. Lloyd-Hamol Limited, of London and Zurich, announce the launching in this country of Thoracin, a new decongestive salve for the symptomatic relief of coughs, colds and respiratory disorders.

▶ The Thoracin formula is based on the same principles that have made Transvasin so successful in the treatment of rheumatic conditions.

▶ Thoracin is composed of esters of substituted hydroxy aromatic derivatives.

▶ Thoracin achieves the effect of the classic counter-irritant remedies—poultices, plasters and cupping — without irritation of the skin.

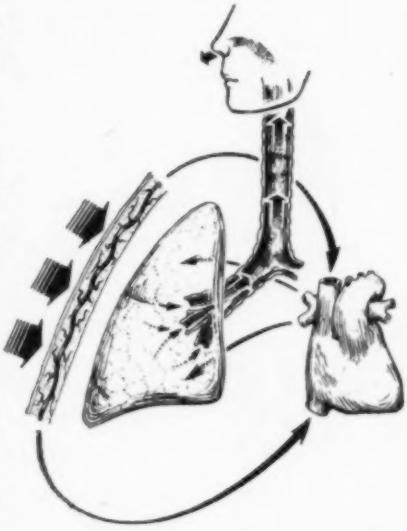
▶ By dispersing œdema Thoracin lessens the formation of mucus in the bronchial passages.

▶ Thoracin contains a new ester of Guaiacol that is entirely free from the evil smell and irritant effect associated with this phenol derivative in its pure form. This ester easily penetrates the skin, and is excreted in the alveoli, where it exerts its well-known action.

▶ Thoracin ensures vasodilation of the superficial skin vessels by the use of esters of nicotinic acid.

▶ Thoracin relieves reflex spasm of the pectoral muscles by the use of the tetrahydrofurfuryl-ester of salicylic acid.

▶ Thoracin brings to the alveoli via the bloodstream the sedative, antispasmodic, and expectorant properties of camphor and eucalyptus.



FORMULA

Phenyl Ethyl Nicotinate	2.0% w/w
Guaiacol Furoate	5.0% w/w
Tetrahydrofurfuryl Salicylate	10.0% w/w
Camphor	3.0% w/w
Eucalyptol	2.0% w/w
Water-Miscible Base to	100.0%

THORACIN is available in 1 oz. tubes at 3/4½d plus 7½d. P.T. It is an ethical product and is not advertised to the public. Since a very small quantity is sufficient for each application, the cost of treatment is extremely low.

Samples and literature will be gladly sent on application.

THORACIN

MADE BY THE MANUFACTURERS OF TRANSVASIN

LLOYD-HAMOL LTD., 11 WATERLOO PLACE, LONDON, S.W.1, AND AT ZURICH

The Remedy is Bismuth Carbonate

WHEN an unbalanced diet, an excess of alcohol or anxiety and worry lead to excessive secretion of acid, inflammation of the stomach, and irritation of the gastric mucosa, the result is indigestion. The remedy is Bismuth Carbonate because it effectively neutralises the acid, it eliminates the inflammation of the stomach, it soothes the gastric mucosa.

Full Illustrated Literature and Free Samples on Request to

BISMUTH RESEARCH DEPT.

MINING & CHEMICAL PRODUCTS LTD.

86 STRAND (1st Floor), LONDON, W.C.2

Seasonal illnesses come and go, but there is no season of the year when Tyrosolven Antibiotic-Anaesthetic Lozenges are not a valuable addition to the range of drugs used in throat infections. Tyrothricin, the active principle in Tyrosolven, is effective against a wide spectrum of bacterial flora — haemolytic streptococci, enterococci, vibrioform and fusiform bacilli, and spirochaetes; there are therefore few common mouth infections they will not relieve. Tyrosolven also contains benzocaine, an effective analgesic.

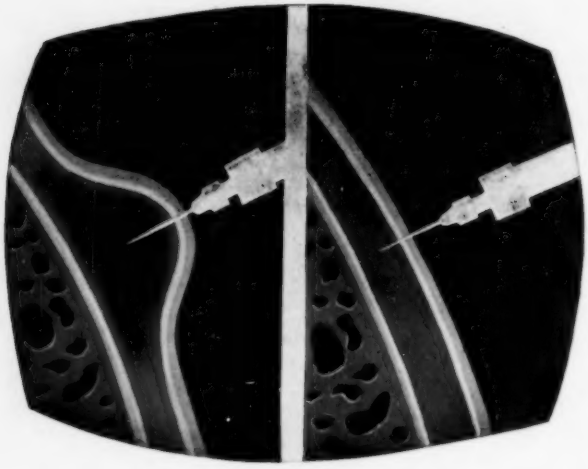
ACTIVE CONSTITUENTS:
Tyrothricin 1 mg., benzocaine 5 mg.

Tyrosolven

Tyrosolven has never been advertised to the public.

William R. WARNER & CO. LTD.,
Power Road, London, W.4.

Packing:
Packs of 20 lozenges; dispensing packs of 250 supplied to chemists at 16/8.



Local anaesthesia

'WYDASE' (freeze-dried Hyaluronidase) enhances the *speed* and *depth* of local anaesthesia, increasing the anaesthetic area by 40%. It is recommended for use in GENERAL SURGERY, and in ORTHOPAEDIC SURGERY for the infiltration of sprains or reduction of simple fractures such as the Colles. The freedom from tissue distortion following its use in PLASTIC SURGERY enables appraisal of results during the progress of the operation.

300 T. R. units of 'WYDASE' (the contents of 2 vials), freshly dissolved in 1 c.c. of cold sterile normal saline, should be added to 50 c.c. of cool anaesthetic solution containing 0.5 c.c. of 1 : 1000 adrenaline.

Available in rubber capped vials containing 150 T. R. units.

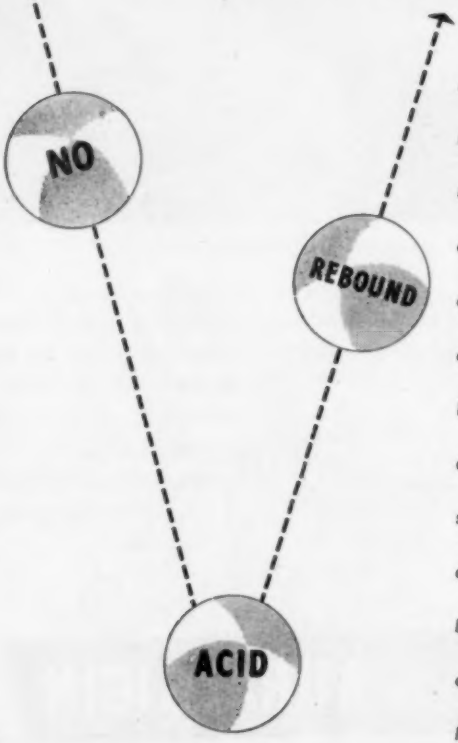
Wyeth

John Wyeth & Brother Ltd.
Clifton House, Euston Road, London, N.W.1

'WYDASE'
Trade Mark
FREEZE-DRIED
HYALURONIDASE

Aluphos Trade Mark

ALUMINIUM PHOSPHATE GEL



Aluphos is a non-constipating non-systemic antacid which cannot cause acid rebound. It is free-flowing and ideally suitable for administration by intra-gastric drip. Further information on request.

A product of

Benger Laboratories

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE · ENGLAND

THIS CHILD is suffering from acute otitis media. No immediate danger, but the parents are anxious. Inflammation and pain must be relieved and infection controlled.

A CLEAR CASE FOR AURALGICIN. Auralgicin—widely known, trusted and prescribed—alleviates pain, reduces the incidence of complications, promotes drainage and encourages resolution. It is quickly and easily administered. Instruction leaflets for the guidance of patients can be supplied to prescribers.

FULLY DESCRIPTIVE literature is available and a Technical Information Service is always at your disposal.

A clear case for AURALGICIN
TRADE MARK

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE
A.3.

A BENGER PRODUCT

A 1000-year old drug takes on a new significance

FOR a thousand years—and probably longer—the value of senna has been recognised. But not until the introduction of Senokot has the *full* therapeutic activity of the drug been made available and its re-educative effect demonstrated.

CLINICAL EVALUATION

"A reliable, completely satisfactory preparation of senna."
Brit. Encycl. Med. Pract., Int. Suppl., March, 1954.

"Constant in action, produces no discomfort, and has no after-constipating effect." *Medical Press, June 9, 1954, p. 523.*

"A valuable ally in the cure of chronic constipation."
Practitioner, March, 1953, p. 272.

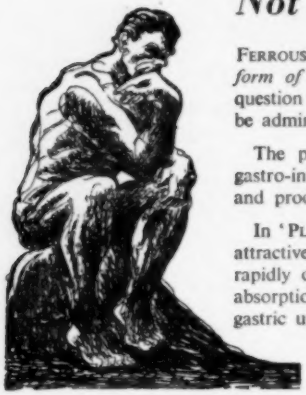
Senokot Regd

STANDARDISED SENNA GRANULES

CATEGORY 3 : Joint Committee on Prescribing

PACKINGS—2 oz., 6 oz.; and 2 lb. (Tax Free).

WESTMINSTER LABORATORIES LTD., CHALCOT ROAD, LONDON, N.W.1



Not whether but how

FERROUS SULPHATE *is now recognised as the most efficient form of iron treatment for hypochromic anæmias.* The question is therefore not "*whether*" but "*how*" it should be administered.

The preparation should not be too bulky, nor cause gastro-intestinal upset, yet it must disintegrate quickly and produce maximum hæmatopoietic response.

In 'PLASTULES' ferrous sulphate is presented in its most attractive form—in a semi-solid base in a capsule which rapidly dissolves in the stomach, thus ensuring maximum absorption. 'PLASTULES' induce a rapid response without gastric upset.

'PLASTULES' *are available in four varieties: Plain; with Hog Stomach; with Folic Acid; and with Liver Extract*

'PLASTULES' *Hæmatinic Compound*

Trade Mark

JOHN WYETH & BROTHER LTD., CLIFTON HOUSE, EUSTON ROAD, N.W.1

Wyeth

Foremost among the tonic restoratives

A special formulation, its delicate flavour rendering it acceptable to the most fastidious palate and representing Vitamin B_1, Liq. Extract of Malt, the Glycerophosphates of Iron, Magnesium and Potassium, and Pepsin, together with Strychnine Hydrochloride 1/200 grain in each fluid drachm. It is indicated in devitalized conditions as it improves appetite and increases mental and physical activity

Available in 4-oz.; 8-oz. 16-oz.; 40-oz. and 80-oz. bottles

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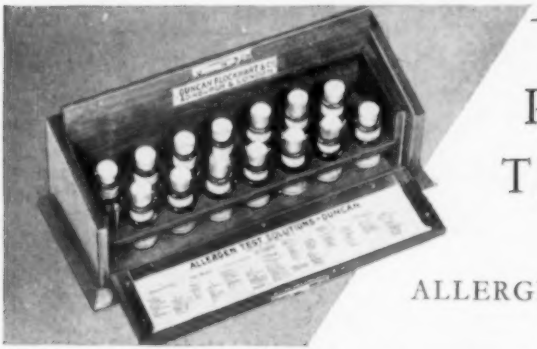

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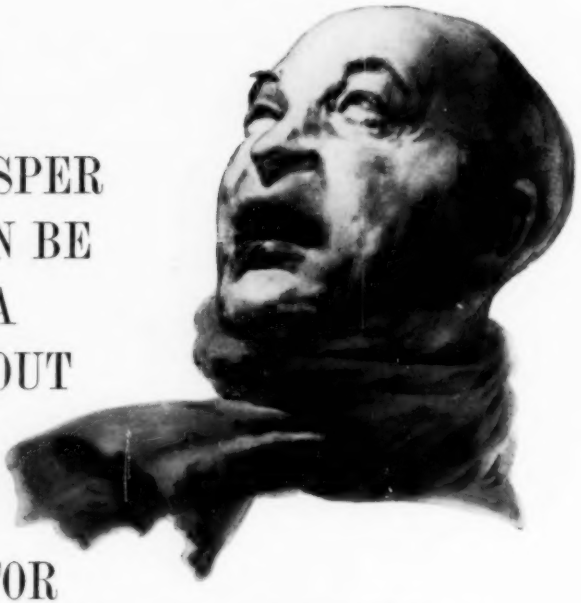

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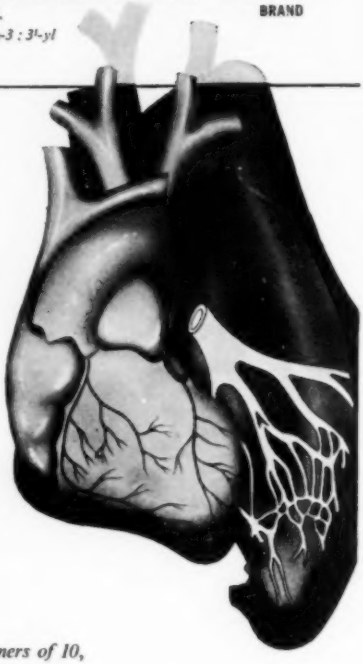

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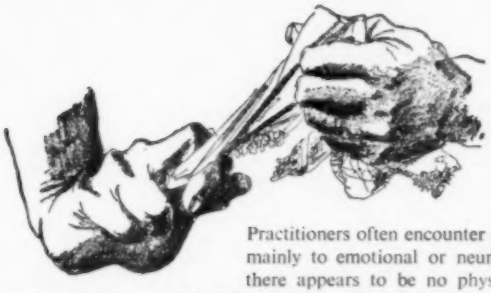

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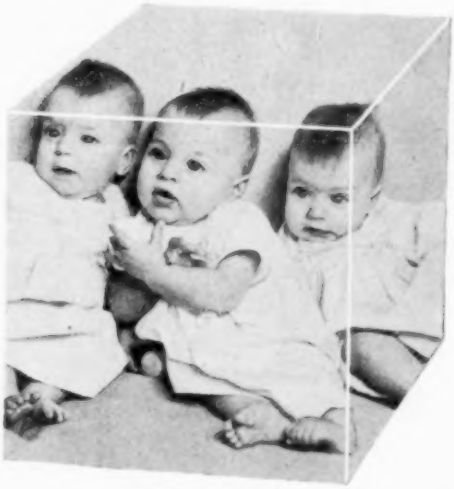

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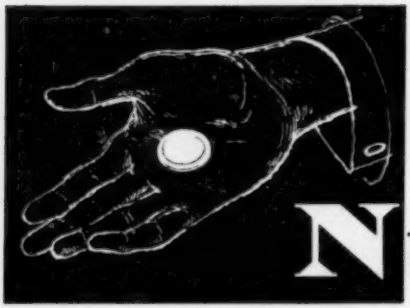
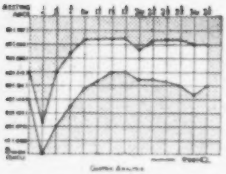
Mrs. Rew, a Cheltenham mother of 6-month-old triplets, has given Bovril Brand Weaning Food to her babies for several months. At birth the three babies weighed 10½ lbs.; they have now reached normal weight.

Bovril Brand Weaning Food is made in four varieties: Mixed Vegetable, Tomato, Spring Cabbage and Carrot. A four-cube carton costs only 6*d*.

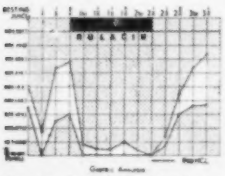


Nulacin

for milk-alkali drip therapy without inconvenience



Superimposed gruel fractional test-meal curves of five cases of duodenal ulcer



Same patients as in Fig. 1, two days later, showing the striking neutralizing effect of sucking Nulacin tablets (3 an hour). Note the return of acidity when Nulacin is discontinued.

The use of milk-alkali drip therapy in establishing and maintaining a state of gastric anacidity has for many years been accepted as a standard practice in the treatment of peptic ulcers.

Such a continuous antacid effect could only be achieved by administering the drip through a tube, with its attendant inconvenience and discomfort to the patient. Nulacin tablets, held in the buccal cavity, give continuous neutralization without inconvenience or discomfort.

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Beginning half-an-hour after food, a NULACIN tablet should be placed in the mouth and allowed to dissolve slowly. During the stage of ulcer activity, up to three tablets an hour may be required. For follow-up treatment, the suggested dosage is one or two tablets between meals.

NULACIN tablets are not advertised to the public and have no B.P. equivalent. May be prescribed on E.C.10. The dispensing pack of 25 tablets is free of Purchase Tax. (Price to pharmacists is 2/-.) Also available in tubes of 12.

NULACIN tablets are prepared from whole milk combined with dextrins and maltose, and incorporate Magnesium Trisilicate 3.5 grs.; Magnesium Oxide 2.0 grs.; Calcium Carbonate 2.0 grs.; Magnesium Carbonate 0.5 grs.; Ol. Menth. Pip. q.s.

BIBLIOGRAPHY:

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Medical Treatment of Peptic Ulcer. *Med. Press*, 27th February 1952, 195-199.
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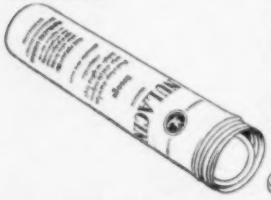
Further Studies on the Reduction of Gastric Acidity. *Brit. Med. J.*, 23rd January 1954, 183-184
Clinical Investigation into the Action of Antacids. *The Practitioner*, July 1954, 173:46

NULACIN

Nulacin is available throughout the British Commonwealth, in the U.S.A. and many other countries. It is known as Nulactin in Canada and Sweden.



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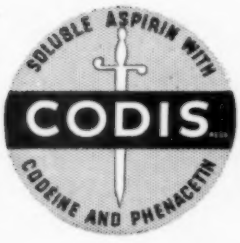
soluble aspirin with codeine phosphate and phenacetin

Codis presents a familiar grouping of analgesic drugs; aspirin, phenacetin, codeine phosphate; with an important advantage. The "aspirin" in Codis is rendered soluble, as in 'Solprin'.

Placed, uncrushed, in water, a Codis tablet disperses in a matter of seconds to form a solution of calcium aspirin and codeine phosphate with finely suspended phenacetin. The chance of irritation of the gastric mucosa by undissolved particles of aspirin is thus minimised.

Codis is recommended for all those conditions for which Tab. Codein. Co. B.P. would be prescribed. It has the added advantages of greater ease of administration and far less likelihood of aspirin intolerance, while the rapid absorption of the soluble aspirin promotes prompt relief.



COMPOSITION

Each Codis tablet weighs 11·45 *gr. and contains:— Acid. Acetylsalicyl. B.P.* 4 *gr., Phenacet. B.P.* 4 *gr., Codein. Phosph. B.P.* 0·125 *gr., Calc. Carb. B.P.* 1·2 *gr., Acid. Cit. B.P. (Exsic.)* 0·4 *gr.*

Codis is not advertised to the public.

N.H.S. basic price for 300 tablets in distinctive gold foils of 6 tablets each, 16/6 per box.

OTHER SIZES—Packs of 20 tablets (in bottles or foil).

RECKITT & COLMAN LTD., HULL AND LONDON. (PHARMACEUTICAL DEPT. HULL).

... the RECURRING problem of the peptic ulcer patient

In many instances, Roter tablets provide effective control of peptic ulcer when other forms of therapy have proved unsatisfactory. Stringent dietary measures are seldom necessary. Hospitalisation or surgical intervention is often obviated.
Extended clinical trials justify the use of Roter tablets in all cases of chronic gastric and duodenal ulcer. Usually, pain and nausea are rapidly dispelled ; healing is accelerated ; the patient is enabled to carry on a normal mode of living without anxiety or discomfort.
Roter tablets may well be the answer to the recurring problem of your peptic ulcer patients.
We will be pleased to forward, on request, literature and a full trial supply.

ROTER **IN PEPTIC ULCER**

Packings: *Tins of 40, 120, 640; and dispensing size, 720 (P.T. Free).*

F.A.I.R. LABORATORIES LIMITED
179 HEATH ROAD, TWICKENHAM, MIDDLESEX
Telephone : POPesgrove 2028

New

FIRST SAFE AND EFFECTIVE INTRAMUSCULAR IRON

BENGER LABORATORIES, who introduced the first intravenous iron preparation, now present a new and equally effective iron complex for intramuscular administration.
ITS NAME IS IMFERON. The introduction of this new compound considerably simplifies the control of iron deficiency anaemias in both hospital and general practice.

Note these advantages . . .

★ **Imferon** is the first safe and effective iron preparation for intramuscular injection—equally suitable for general practice and hospital use.

★ **Imferon** is well tolerated. Reactions of the kind which have been reported with saccharated oxide of iron have not been observed.
AMPOULES 2 ml. (100 *mg. Fe.*)
BOXES 10 and 100.

★ **Imferon** produces a haemoglobin response identical with that obtained by saccharated oxide of iron. The response is thus predictable.

★ **Imferon** provides the equivalent of 250 m.g. of iron per 5 ml. injection; fewer injections are therefore necessary to administer the calculated total dose.
AMPOULES 5 ml. (250 *mg. Fe.*)
BOXES 5 and 50.

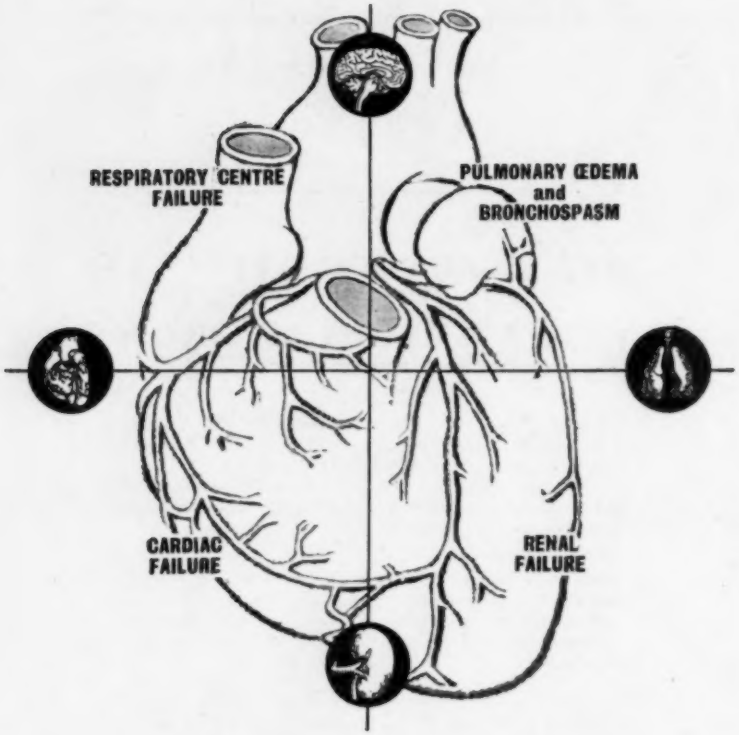
Fully-descriptive literature on request.
A Technical Information Service is at your disposal.

Imferon TRADE MARK

Iron-Dextran Complex

A PRODUCT OF
BENGER RESEARCH

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE



Cardophylin provides **4** point coverage

in controlling the various complications of heart failure

Benger Laboratories

Cardophylin is presented in tablets, suppositories and ampoules for intramuscular and intravenous administration. Literature is available on request.

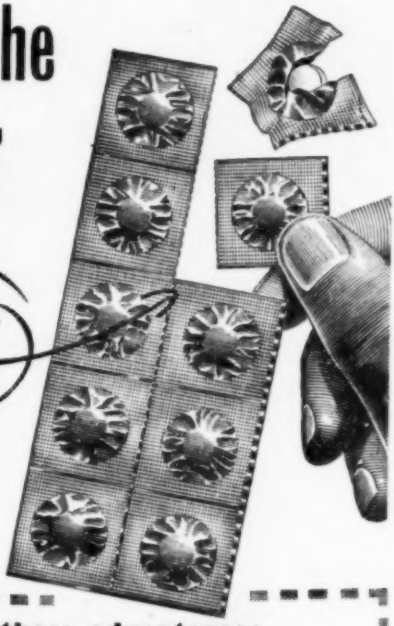
Cardophylin—manufactured by Whiffen & Sons Ltd., is distributed by

BENGER LABORATORIES LIMITED • HOLMES CHAPEL • CHESHIRE • ENGLAND

TABILLIN in the new 'Foil-Pac'

This new method of packing protects each tablet until used

individually sealed tablets —detached as required



—a most important consideration in oral penicillin therapy, which is now established as a satisfactory method of systemic administration.

Tabillin offers these advantages:

1 Tabillins, being individually sealed, are protected against contamination and loss of potency.

2 Each dose of Tabillin is protected until required—therefore superior to liquid preparations.

3 Any quantity of Tabillin can be prescribed and dispensed without losing the advantages of individually-sealed protection. Wastage is eliminated.

4 Tabillins contain soluble penicillin which gives higher and more persistent blood-levels than do insoluble penicillin salts.

5 'Foil-Pac' Tabillins are economical. Available at no greater cost than unwrapped tablets.

Whenever Oral Penicillin Therapy is indicated, Tabillin is the preparation of choice.

TABILLIN *Penicillin Tablets B.P.*

Tablets of 100,000, 200,000, 400,000 and 500,000 I.U. Containers of 10 and 100 tablets.

Descriptive literature from Medical Dept., Boots Pure Drug Co. Ltd., Nottingham 8199

Boots

Congested?

Decongested!

We have no panacea to offer those wrestling with the traffic congestion of our cities but Karvol Inhalant Capsules will clear the respiratory thoroughfare. In the common cold, in bronchitis and bronchial catarrh and in more serious conditions too, of the pharynx, bronchi and bronchioles the town dweller, particularly, living in a fog and soot-laden atmosphere may turn to Karvol with safety and confidence.

Crookes KARVOL INHALANT CAPSULES

Bottles of 20 capsules. *May we send you samples?*

THE CROOKES LABORATORIES LIMITED · PARK ROYAL · LONDON · N.W.10

Relief

from allergy . . .

BENADRYL, probably one of the most potent histamine antagonists, has proved to be of great value in the treatment of hay-fever, urticaria, vasomotor rhinitis, angio-neurotic oedema and, in the majority of cases, gives long looked-for relief in the skin infections and pruritic conditions associated with allergy. The Parke Davis range of products which include Benadryl provide for oral administration, topical and ophthalmic application and a solution for injection where, in acute allergic conditions, rapid action is required.

BENADRYL CAPSULES
BENADRYL ELIXIR
BENADRYL CREAM
CALADRYL
Cream and Lotion
BENADRYL OPHTHALMIC
BENYLIN EXPECTORANT
BENADRYL EMPLETS
BENADRYL PARENTERAL
BENA-FEDRIN
Nasal Decongestant

BENADRYL

A SUCCESSFUL ANTIHISTAMINE

Parke, Davis & Company Ltd. (Inc. U.S.A.)
HOUNSLOW · MIDDLESEX
Tel.: Hounslow 2361.

Specific for the prevention and treatment of Napkin Rash

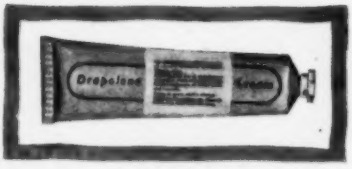
DRAPOLENE CREAM was formulated specifically for the treatment and prophylaxis of urinary ammonical dermatitis. The distress and anxiety of this state have not been experienced when DRAPOLENE has been used as a preventative measure.

Reports received from many Infant Welfare Centres have stated that successful results have been obtained in both mild and severe forms of napkin rash, **the condition clearing completely in four to six days.**

DRAPOLENE also possesses cleansing properties which beneficially contribute to napkin toilet, thereby minimising the risk of aggravating the already hypersensitive area.

FORMULA
Benzalkonium chloride, 0.01% in a water miscible base.

PRICES
2oz. tubes: 3/- each.
4lb. dispensing jars: 16/- per lb.



DRAPOLENE CREAM

PRESCRIBE BY NAME

CREWE
Telephone Crewe 3251-5

CALMIC LIMITED

LONDON
2 Mansfield Street, W.1
Telephone: LANgham 8038-9

The ox bile salts, sodium taurocholate and glycocholate, are present in a tablet of Veracolate to the amount of 1.07 grains. The official dose of bile salts is 2 to 6 grains, and the recommended dose of 3 tablets daily therefore places Veracolate in the officially recommended therapeutic range. Veracolate stimulates the secretory activity of the liver and is used in chronic cholecystitis, "liverish" and "bilious" attacks, and constipation.

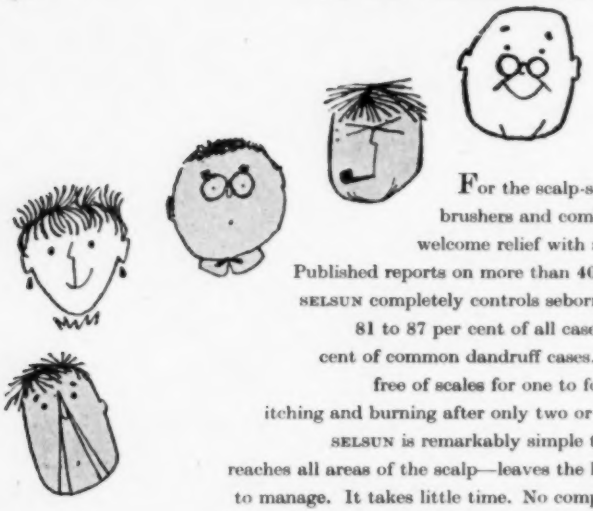
FORMULA
Sodium taurocholate & glycocholate, each 1.07 gr., ext. cascara sagrada, 1.00 gr., phenolphthalein 0.50 gr., oleoresin capsicum 0.04 gr.
PACKING
Bottles of 50 & 100 tablets; bottles of 500 tablets for dispensing purposes only at 16/8d. not subject to P.T.

Veracolate

No Warner preparation has ever been advertised to the public.

WILLIAM R. WARNER & Co. Ltd.,
Power Road, London W.4.

who have seborrhoeic dermatitis of the scalp



For the scalp-scratchers, shoulder-brushers and comb-clutterers, there's welcome relief with SELSUN Suspension. Published reports on more than 400 cases[1-3] show that SELSUN completely controls seborrhoeic dermatitis in 81 to 87 per cent of all cases, and 92 to 95 per cent of common dandruff cases. It keeps the scalp free of scales for one to four weeks—relieves itching and burning after only two or three applications. SELSUN is remarkably simple to apply, it quickly reaches all areas of the scalp—leaves the hair clean and easy to manage. It takes little time. No complicated procedures or messy ointments. In 2 and 4 fluid ounce bottles with full directions on special label.

Abbott

SELSUN
Regd.
Suspension

(SELENIUM SULPHIDE, ABBOTT)

1 (1952), *Arch. Dermat. & Syph.* 65:228, *February*.
2 (1951), *ibid.*, 64:41, *July*.
3 (1952), *J. Missouri Med. Assn.*, 49:911, *November*.

ABBOTT LABORATORIES LTD · PERIVALE · GREENFORD · MIDDX

Treatment of the Streptococcal Throat

'PONDETS' Penicillin are a new and ingenious vehicle for local oral penicillin therapy, that combine the striking advantages of extreme palatability with prolonged action. Each 'Pondet' contains 5,000 international units of crystalline potassium penicillin-G in a delicious hard, fruit, toffee-like base that completely masks the bitter taste of penicillin.

Because of the nature of their hard base, 'Pondets' dissolve slowly and uniformly, supplying an uninterrupted high concentration of penicillin to infected areas of the oro-pharyngeal mucosa.

INDICATED in minor superficial oral infections due to penicillin sensitive organisms ranging from the 'Streptococcal Throat' to the less common Vincent's infection and recommended for routine prophylactic use following Tonsillectomy.

Individually wrapped in bottles of 20.

Children accept 'Pondets' as readily as a sweet, and they are particularly useful in controlling throat infections in juvenile communities.

'Pondets' *Trade Mark* **PENICILLIN TROCHES**

JOHN WYETH & BROTHER LTD., CLIFTON HOUSE, EUSTON ROAD, N.W.1 Wyeth

Bronchitis Winter Cough and Sequelæ

There is a vast amount of evidence of the most positive character proving the efficacy of Angier's in sub-acute and chronic bronchitis. It not only relieves the cough, facilitates expectoration, and allays inflammation, but it likewise improves nutrition and effectually overcomes the constitutional debility so frequently associated with these cases. Bronchial patients are nearly always pleased with Angier's and often comment upon its soothing, "comforting" effects. The unique soothing properties of Angier's, its favourable influence upon assimilation and nutrition, and its general tonic effects, make it eminently useful both during and after influenza. It has a well-established reputation for efficiency in relieving the troublesome laryngeal or tracheal cough, correcting the gastro-internal symptoms and combating the nervous depression and debility.

Angier's Emulsion

THE ANGIER CHEMICAL COMPANY LIMITED, LONDON S.E.1. LABORATORIES: SOUTH RUISLIP

A versatile drug*

Depressive States

Overweight

Narcolepsy

Post-encephalitic Parkinsonism

Alcoholism

Enuresis

Behaviour Disorders in Children

Petit Mal

'Dexedrine'

Each tablet contains 5 mg. dextro-amphetamine sulphate

SMITH KLINE & FRENCH INTERNATIONAL CO.
Represented by
Menley & James, Ltd., Coldharbour Lane, London, S.E.5
Tel: BRIxton 7851

'Dexedrine' is a registered trade mark

6IP114

Effective, non-sensitizing tar therapy for

CHRONIC LESIONS OF THE SCALP

SEBBIX

contains purified fractions of tar, sulphur and salicylic acid in a specially formulated water miscible base. It is effective in the crusted or scabbed stage of seborrhoea capitis in adults and infants, and in psoriasis of the scalp.

* *Persistent Dandruff*

SEBBIX SHAMPOO

A tar shampoo with an active bactericidal principle in a special soapless base, formulated for use with SEBBIX. An ideal general-purpose shampoo for recommendation to patients for the treatment of persistent dandruff.

Containing 2% Salicylic Acid
3% Sulphur
Purified fraction equivalent to 10% crude coal tar

AVAILABLE ON E.C.10

Further information can be obtained from the Medical Department,

GENATOSAN LTD.

Loughborough, Leicestershire

The manifestations of a functionally disordered gastro-intestinal tract, agonising at their worst, are at their least a source of social embarrassment which can be distressing in the extreme. Busy people, who must often go long hours without time for food, have good reason to hail the advent of an effective anti-spasmodic which will, in more senses than one, quieten their yearning bowels.

MERBENTYL REGD.

distributed in the United Kingdom & Eire by
RIKER LABORATORIES LIMITED, LOUGHBOROUGH, LEICS.
for the Wm. S. Merrell Company, London.

MERBENTYL *Tablets each containing 10 mg. Diethylaminocarbethoxybicyclohexyl hydrochloride.*

MERBENTYL WITH PHENOBARBITONE *Tablets each containing 10 mg. Diethylaminocarbethoxybicyclohexyl hydrochloride and 15 mg. Phenobarbitone.*

Each in bottles of 50 and 250 tablets. The basic N.H.S. cost of treatment is less than 5d. a day.

A Superior Buffered Analgesic

'ALASIL' TABLETS—the improved form of salicylate medication—provide the efficient analgesia expected from their content of aspirin. Their superior acceptability derives from their content of a reliable buffer which minimizes the tendency to gastric irritation sometimes caused by the use of aspirin alone.

Advantages

'Alasil' is an advanced sedative and antipyretic; it does not tend to induce gastric irritation; because of its high tolerability, it may be used for long-term administration even to those with sensitive stomachs, and to children.

Composition

'Alasil' Tablets contain the recognized antacid corrective, 'Alocol' (Colloidal Aluminium Hydroxide), which permits their sedative principle, acetylsalicylic acid, to exert its action with minimal risk of side-effects.

Packs & Prices

Symptomatic pain generally; rheumatism, fibrositis, lumbago, headache, dysmenorrhoea; dental pain.

Indications

TO PHARMACISTS (*P.T. exempt for dispensing*)
Standard size: 1000 in 250 bottles, 30/8.
'Juvenile' size: 375, 6/6; 750, 11/3; 1,500, 21/6.

NHS SCRIPTS

Alasil

Sample and literature on request to **A. WANDER LTD., 42 UPPER GROSVENOR ST., LONDON W.1**

ALASIL JUVENILE TABLETS

Alasil 'Juvenile' Tablets specially sized for children, and neither coloured nor flavoured, are packed in tubes bearing dosage-for-age instructions.

M.391

Visit Stand No. 112 at the London Medical Exhibition, Royal Horticultural New Hall, Greycoat Street, London, S.W.1, November 15-19.

In the Service...

Research

The House of Wander continues to maintain its advanced position in pharmaceuticals and quality food products because the standardization of active ingredients during manufacture is backed by careful control and investigation in its extensive Research Laboratories.

In Quality

The Wander Research Laboratories have made useful contributions in the fields of dietetics, nutrition and vitamins. Their wide experience and up-to-date laboratory facilities help to maintain the high quality of Malt Extract and Cod Liver Oil (Wander) the vitamin content of which exceeds that of the analogous B.P. preparations.

The special consideration of physicians when prescribing a malt and oil preparation is that of vitamin values. Comparative studies prove that to prescribe "Wander Brand" is to specify malt extract and cod liver oil of the finest possible quality.

In the Service of Medicine

Careful control and investigation help to maintain "Wander Brand" in the forefront of its class. Moreover, with all its special advantages, "Wander Brand" costs no more than some malt and oil preparations with a lower vitamin content.

℞ **Malt & Oil** (WANDER)

Visit Stand No. 112 *at the London Medical Exhibition, Royal Horticultural New Hall, Greycoat Street, London S.W.*1. *November* 15-19

M.352

new..

effective local antibiotic therapy –minimal risk of sensitisation

'Polyfax' combines 'Aerosporin' brand Polymyxin B Sulphate with Bacitracin in a new antibiotic ointment of *very wide antibacterial range*. 'Polyfax' has a prominent place in clinical practice because

- **'Polymyxin' is lethal to many gram-negative organisms, particularly** *Ps. pyocyanea.*
- **Bacitracin is effective against gram-positive organisms.**
- **Drug resistance to polymyxin is unknown, to bacitracin very rare.**
- **Penicillin-resistant strains often succumb to bacitracin.**
- **Risk of skin sensitisation is minimal.**
- **Local absorption is insignificant.**
- **Subsequent systemic use of antibiotics is not prejudiced.**
- **'Polyfax' is so formulated that its antibiotic components are stable and readily diffusible.**

'Polyfax' is non-irritating and may be applied for long periods if necessary. It is available in tubes of 20 gm. for topical application and in tubes of 4 gm. with special nozzle for ophthalmic use.

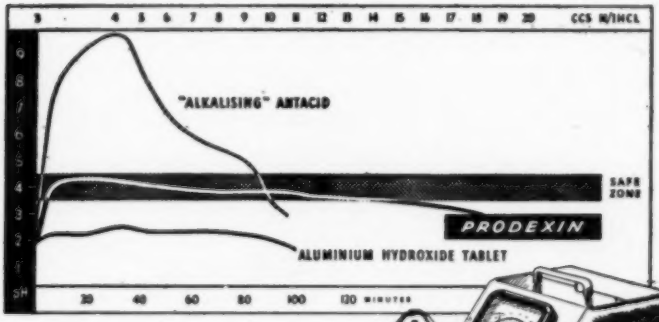
'Polyfax'

Polymyxin B Sulphate Ointment

BURROUGHS WELLCOME & CO. *(The Wellcome Foundation Ltd.)* **LONDON**

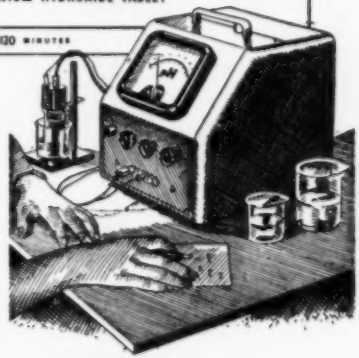
A New development
providing *CONTROLLED* antacid therapy

Prodexin is a new product containing aluminium glycinate, and belongs to the buffer group of antacids. It depends for its action upon the slow release, on hydrolysis, of active aluminium hydroxide gel and glycine (amino acetic acid). Glycine rapidly raises the pH to 2, sparing the aluminium gel for the later stage of raising it into the "safe zone" of pH 3·5 to 4·5. Prodexin maintains an equable gastric environment for long periods without alkalisation.



Prodexin provides a convenient, economical and safe treatment for HYPERACIDITY and PEPTIC ULCER.

The tablets, sucked one at a time, maintain the pH of the stomach contents within the "safe zone" for up to two hours. With Prodexin there is no risk of acid rebound or alkalosis. Prodexin tablets are pleasant to suck and they do not form gritty particles in the mouth or give rise to constipation.



Each tablet contains:—
Aluminium glycinate . . . . . 0·9 gramme.
(*dihydroxy aluminium aminoacetate*)
Light magnesium carbonate . . . . 0·1 gramme.
The basic N.H.S. cost of treatment at the rate of 6 Prodexin tablets daily is 8½d.

PRODEXIN

Manufactured in the laboratories of

C. L. BENCARD LIMITED

MINERVA ROAD · PARK ROYAL · LONDON · N·W·10

The night passes serenely to a fresh awakening...
Since the original synthesis of 'Amytal' over thirty years ago, Eli Lilly & Company has been closely associated with the further development of the barbiturates.
To-day, as a result of further research by Lilly, the physician has an extensive range of barbiturates from which to choose the drug most suited to his case.
Included in the Lilly range of Barbiturates are—
'PULVULES' brand filled capsules.
'SECONAL SODIUM'
brand Quinalbarbitone Sodium.
Quick onset — short duration.
gr. ¾ and gr. 1½.
'SODIUM AMYTAL'
brand Sodium Amylobarbitone.
Medium onset — medium duration.
gr. 1 and gr. 3.
'TUINAL'
brand Quinalbarbitone Sodium with Sodium Amylobarbitone.
Quick onset — medium duration.
gr. 1½ and gr. 3.
and Tablets
'AMYTAL'
brand Amylobarbitone.
Medium onset — moderately long duration.
gr. ½, gr. ¾, gr. 1, gr. 1½ and gr. 1½.
Barbiturates
Lilly
TRADE MARK
ELI LILLY & COMPANY LIMITED, BASINGSTOKE, ENGLAND

THE PRACTITIONER

No. 1037 NOVEMBER 1954 Volume 173

THE MONTH

The Symposium

'DURING the last five years between 16 and 29 per cent. of patients visited at home were suffering from a disease caused, or possibly caused, by a virus'. If any special justification were required for devoting an entire symposium to virus disease, it is to be found in these figures which are quoted from Dr. G. I. Watson's article on 'Virus disease in general practice'. This uprising of virus disease to the status of one of the major hazards of life is perhaps the most striking feature of modern medicine. In the symposium this month we have aimed at epitomizing and assessing our present knowledge of the subject, with the emphasis on the more practical aspects of the problem. It is significant that three of the seven contributors to the symposium are on the staff of the National Institute for Medical Research, whilst Professor Van den Ende, who contributes the introductory article on 'Our present understanding of viruses', was also on the staff of the Institute before he returned to the University of Cape Town. The country has every reason to be proud of the outstanding contributions which workers at the Institute have made to our knowledge of viruses—contributions which have established for the Institute an international reputation in this vitally important field.

Although the conquest of virus disease is not yet in sight, there are good grounds for sober optimism. No therapeutic agent has so far been discovered that has an appreciable effect on any of the viruses pathogenic to man. On the other hand, understanding of their structure and metabolic processes is advancing steadily, if slowly, and the prospects of bringing them under control by means of vaccination are improving. Effective vaccines against influenza have been produced, even though their efficacy varies from epidemic to epidemic. In the case of poliomyelitis, Dr. Bradley rightly introduces a note of caution, but the possibility of an effective and safe vaccine being produced for this disease is much brighter than it has ever been before.

Medical Education

LAST year the World Medical Association convened in London a World Conference on Medical Education. The proceedings of these meetings have now been published (Oxford University Press, price 60*s*.). They present as comprehensive a picture as has yet been published of the variegated maze through which the medical students of the world have to pass before they can attain the status of practitioners of medicine. Fortunately, little attempt has been made to discipline the contributors. Hobby horses are ridden, sometimes with

Quixotic ferocity; the dear old platitudes rear their hoary heads; the old arguments are bandied about concerning the length of the preclinical period, the relative merits of whole-time and part-time teachers, the place of the specialties in the curriculum. Against this background of dogmatism and contradiction stand out the contributions which have something new and fresh to say: the interesting experiment in teaching general practice in Richmond, Virginia, for instance, and the integration of anatomy and physiology in Birmingham.

Because of its very diffuseness and incoordination, this is an infinitely better picture of medical education than any of the reports on the subject with which we have been deluged during these post-war years. This is medical education in the raw—as it is promulgated not as the theorists think it should be done. In its contrasts and contradictions it mirrors the individualism of clinical medicine. To produce an internationally uniform medical curriculum would be as ludicrous as the attempts of the more unbalanced selectors to discover the standard medical student. Provided certain fundamentals are always observed, the practice of medicine must be as variegated in its trimmings as the flags of the nations of the world. So far as we in Great Britain are concerned, one lesson is clear from a perusal of these pages. For the maintenance of that high standard of clinical practice which has always been the hallmark of British medicine, the length of the medical curriculum must be cut to five years, followed by one year's compulsory service in hospital. Only by so reducing the course can all the frills be discarded which the non-clinicians and administrators have added to the curriculum during the last two decades. They are not only not essential, they have become a positive danger to the training of a doctor who is both a cultured humanist and a sound and understanding clinician.

Human Experimentation

EVERY post-war period tends to be characterized by a lowering of respect for the sanctity of human life. In the case of the post-1939-45 period this tendency has been enhanced by the aggressive promulgation of certain ideological trends based upon the belief that the interests of the individual are subservient to those of the 'State' of which he is a member. This cynical perversion of that love of one's country, which is one of the most deep-rooted instincts in mankind, reached its sadistic climax in the orgy of race-extermination in Nazi Germany during the 1939-45 War, when thousands of political prisoners were sacrificed on the altar of medical research. The aftermath of this black spot in the history of medicine is still causing concern on the Continent, and the whole problem of the extent to which human beings can be used for experimental purposes was the subject of discussion at the 8th General Assembly of the World Medical Association in Rome last month.

Although the problem is not one which is ever likely to assume an acute form in these Islands, it is one which must ever be borne in mind. To a

certain extent, every time we treat a patient we are carrying out an experiment, but the mounting momentum of medical progress is an ever-increasing temptation to submit our patients to investigational and therapeutic devices which have not yet been thoroughly explored, and which may lay our patients open to risks to life or health which are not justified by the moral code which we have accepted as the basis of all good medical practice. Human experimentation there must always be, but the individual doctor, whether physician or surgeon, consultant or general practitioner, in the home or in the most elaborate clinical research institute in the world, must always be reminding himself of that modern paraphrase of the Hippocratic Oath, contained in the Declaration of Geneva: 'The health of my patient will be my first consideration'. Should he always bear this in mind, as well as Johnson's dictum—'Integrity without knowledge is weak and useless, and knowledge without integrity is dangerous and dreadful'—he is not likely to go far wrong in his duty.

Medical Tablets

At the present moment, when tablets constitute approximately one-third of all medicines dispensed in this country, it is interesting to recall what a relatively recent innovation the tablet is in medical practice. It was in 1843 that a patent was granted to William Brockendon, a North Country chemist, for a tablet-making machine, but it was not until 1885 that an official monograph describing a drug in tablet form was included in the *British Pharmacopœia*—under the title of 'Tabellæ Trinitrini'. For sixty years, as Mr. T. C. Denston, Secretary of the British Pharmacopœia Commission, pointed out in a paper read before the Pharmaceutical Conference in Oxford this summer, this essential ingredient of the cardiologist's armamentarium was the only representative of this class of medicament in the Pharmacopœia. Since then, the position has changed rapidly. The Seventh Addendum to the *British Pharmacopœia* 1932, published in 1945, described 35 tablets, and this number was increased to 63 in the 1953 Pharmacopœia. The *British Pharmaceutical Codex* 1954 will include 72 monographs on tablets. The same trend is occurring in other countries. Thus, the United States Pharmacopœia, which included no tablets until 1936, when one monograph was added, now has 92 monographs, whilst the Danish Pharmacopœia 1948, with Addendum 1952, describes 99 tablets. On the other hand, the pharmacopœias of Argentine, Belgium, France and Turkey contain no monographs on individual tablets, although they each contain a general monograph on the subject.

In spite of their many practical advantages, the advent of tablets was greeted with considerable scepticism by pharmacists, and as late as 1895 the *Pharmaceutical Journal* published an editorial deprecating their sale and predicting that they had had their day. Although there are still some difficulties in evolving comprehensive official standards, manufacturing processes have been so improved that today a tablet can be produced by mass production methods with an accuracy of dosage and an elegance of shape and texture

that compare favourably with the most refined of hand-prepared mixtures. There can be little doubt that, as one speaker commented at the British Pharmaceutical Conference, 'although tablet history is comparatively short, the tablet would appear to be assured of a long future'.

'Those Damned Dots'

MATHEMATICS and medicine have always been uneasy bedfellows, and during these latter years many a clinician on opening his medical journals has paraphrased Lord Randolph Churchill's comment on the decimal system: 'I never could make out what those damned dots meant'. This occupational trait of our profession, in conjunction with our traditional dislike of regimentation, is probably largely responsible for the somewhat frigid reception which we have given to the statistician and his insistence upon controls and to the administrator with his multiplication of forms. Whether we like it or not, however, documentation is coming to play an increasingly important part in the evolution of medicine and, whilst the administrator, whether in Savile Row or in the local hospital or town hall, must never be allowed to control the practice of medicine, it is clear that if our patients are to receive the full benefits of modern medicine, the clinician must be prepared to keep his records in such a manner that they can be used for investigational purposes.

The possible scope of investigation based upon vital statistics, local authority statistics, hospital and general practice statistics is admirably reviewed in a paper on 'Medicine and medical services in the United Kingdom', by B. Benjamin, B.Sc., F.I.A., Statistician at the General Register Office, which has been reprinted from the *Journal of the Royal Statistical Society* (Series A [General], Vol. 117, Part II, 1954), and can be obtained from the Royal Statistical Society (price 2*s*.). As Mr. Benjamin rightly points out, 'consciously or unconsciously the teaching of medicine and its practice call for the sifting of a myriad of facts by those very processes of classification and association upon which the statistical method is founded'. His review of the mass of available data and the useful ends to which it could be put in ensuring the best possible utilization of the medical services of the country, is not only clear and authoritative, but also shows an understanding of the problem which faces the practitioner in collaborating in such investigations: 'Valuable information could be obtained accurately and easily by the general practitioners provided that the necessary clerical facilities were made available. But the primary duty of the practitioner is to attend the sick and if his fund of knowledge is to be on loan to the communal health services he will need to be convinced first that this can be done without making an additional and unbearable claim on his time and energy'. A cooperative effort on the part of statisticians and clinicians, carried out in this spirit of mutual understanding, would go far towards enhancing the value of the National Health Service and advancing our knowledge of disease processes and the means whereby the health of the community could be maintained.

OUR PRESENT UNDERSTANDING OF VIRUSES

By M. VAN DEN ENDE, M.B., Ph.D.
Director of the Virus Research Unit, Department of Pathology, University of Cape Town

In the ever-widening field of biological knowledge, our understanding of the nature of viruses is continually undergoing modification. Green (1935), Laidlaw and others conceived them as micro-organisms stripped of independent enzymes and entirely dependent upon the metabolism of their host cells. In spite of the enormous advances in the last decade, it would be bold to suggest that we have widened our concept beyond this, but perhaps an altered emphasis on certain aspects of their behaviour and structure brought about by the application of modern research methods is influencing our interpretation of the nature of viruses.

WHAT IS A VIRUS?

It is now generally agreed that all viruses are 'ultra-microscopic', and since the effective resolving power of the ordinary microscope is approximately 0.2μ, this term implies that viruses are in general less than 0.2μ in diameter. Secondly, viruses can only multiply in susceptible living cells. Whilst these criteria are in a sense arbitrary, they serve effectively in practice to delimit the group. Luria (1953) has defined viruses as 'submicroscopic entities, capable of being introduced into specific living cells and of reproducing inside such cells only'. This definition has the advantage of simplicity, while at the same time it draws attention to a third prerequisite: that the virus has the power of entering the cell from its environs.

THE UBIQUITY OF VIRUSES

Until quite recently virology was the happy hunting-ground of the bacteriologist and pathologist and those viruses pathogenic to man received the closest study. Today this field is attracting many more research workers, whose interests embrace not only human virus diseases but, to a greater extent than formerly, the study of bacterial, plant, animal, and insect viruses.

Physicists, biochemists, geneticists and others are now attracted into the various branches of virology by subjects for research at least as interesting and valuable as medical virology. The students of bacteriophages, for example, have elucidated many steps in the process of intracellular multiplication of viruses; the plant virologists have achieved a degree of purification of plant viruses which would satisfy many of the most exacting chemists; those studying the insect viruses have elucidated the structure of the virus-containing polyhedral inclusion bodies so characteristic of certain virus

diseases in insects, and in the field of animal virology enormous advances have been made in methods of cultivation and purification of viruses and the development of preventive measures against them.

BACTERIOPHAGES

The bacterium-bacteriophage system is probably the simplest host-virus system available to the virologist, for the susceptible host can be cultivated in enormous numbers in a short period of time and its environment can be exactly controlled. Research on bacteriophages has achieved important results in many fields, two of which must be briefly mentioned here: (1) the study of the action of phages of the T series on its susceptible host *E. coli B*, and (2) the study of lysogenicity.

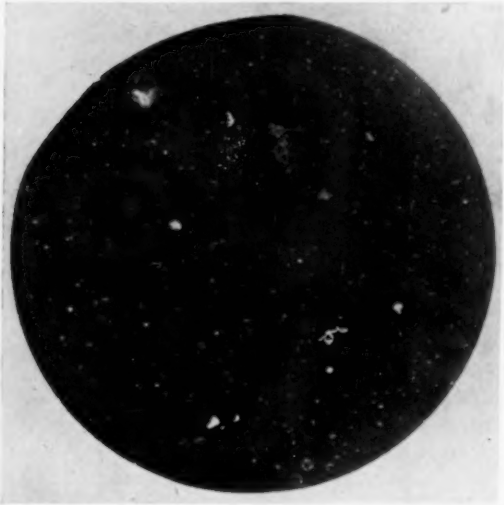


FIG. 1.—Electron microphotograph of a bacteriophage of *Ps. æruginosa*, showing numerous tadpole-shaped phage particles (x 5000). (Photograph: National Institute for Medical Research, London.)

The action of phages of the T series on E. coli B.—For the purpose of this brief review consideration of the studies which have been made with those members of the series which are virulent and therefore lead to rapid destruction of the host bacteria, with consequent lysis of the culture and release of new phage, is probably the most important. Intensive study of a relatively small group of phages by teams equipped with the knowledge and techniques of modern science has revealed previously unidentified properties of the phages, which are now being utilized to study intracellular stages of virus multiplication. For instance, minor but nevertheless constant differences have been observed between variants of the phages T2 and T4. On lysis, host cells infected simultaneously with recognizable variants of those closely related viruses will release phage particles which bear the genetic imprint of both strains of infecting virus (Delbrück and Bailey, 1946; Epstein, 1953).

Much of our knowledge of bacteriophage multiplication has been obtained from the so-called 'one-step' growth experiment, where a single cycle of

multiplication of a 'virulent' phage occurs in its susceptible host (Ellis and Delbrück, 1939). It has been established that the bacteriophage consists largely of nucleic acid and protein, embodied in a particle of definite and constant morphology. Many have the appearance of miniature tadpoles (fig. 1) whilst others are spherical or rod shaped. Its components are immunologically distinct from the constituents of the host and those of other phages. Under appropriate conditions three phases in the multiplication of phage can be defined. First, it finds attachment to specific receptors on the surface of the host cell (Burnet, 1930). Such adsorption is rapid, it soon becomes irreversible and in some cases it is dependent upon the presence of cofactors such as Ca^+ ions or even relatively complex organic substances like tryptophane (Anderson, 1948) in the medium. The phase of adsorption is terminated by the entrance of nucleic acid from the phage into the host cell. The protein component of the phage apparently remains on the surface and therefore appears not to be needed in the initiation of intracellular phage synthesis. At this stage, infective phage cannot be recovered from the host cell even if it is mechanically disrupted, and phage does not in fact reappear until late in the next stage which is the latest period or stage of intracellular synthesis. The third stage, which follows on the latent period, is characterized by abrupt lysis of the infected cells and the release of the phage progeny. The length of the latent period and the amount of phage released per infected bacterium (burst size) are constant for each phage under a particular set of experimental conditions (fig. 2).

Much has been learnt of the processes involved during the latent phase, when intracellular multiplication of phage is taking place. It is noteworthy that, whilst bacterial respiration continues at the normal rate during phage synthesis, the synthesis of bacterial constituents is replaced by that of phage components. The formation of phage constituents such as protein and nucleic acid precedes the appearance of complete phage. Electron microscopy of the contents of phage-infected bacteria has revealed also that the formation of doughnut-shaped bodies which become incorporated into the bacteriophage heads precedes the appearance of mature phage particles (Levinthal and Fisher, 1952; De Mars *et al.*, 1953). Individual constituents therefore are formed separately during the earlier stages of the latent period and are assembled into phage shortly before its release. The picture which is evolving, particularly from the studies of physicists and geneticists, is of the genetic material (nucleic acid) of phage origin dominating the intracellular synthetic processes normally controlled by the host cell's own genes. The exact manner in which replication of individual phage components takes place is controversial but, whatever the method involved, it must give opportunity for the conjugation and separation of genetic material at various stages during synthesis. Whilst the nucleic acid can be regarded as the essential constituents for the phage reproduction, much of what is seen morphologically and structurally in the extracellular stage probably acts

simply as a medium for the transport of the nucleic acid and for giving specific lethal attachment to the susceptible host cell. It is of interest that the so-called colicines, which are released by certain carrier strains of *E. coli* and which are lethal to susceptible strains of this species, possess the properties that can be attributed to incomplete (nucleoprotein-free) phages. Thus, they gain specific attachment to susceptible cells to which they are lethal, but in which they undergo no multiplication.

Lysogenicity.—That phage-host interaction does not always lead to destruction of the host has long been known. The most prolific source of new phages is from so-called lysogenic strains of bacteria. Such strains though infected by phage do not undergo lysis, and the presence of the phage can only be detected by its action on a different but closely related strain of bacteria which is susceptible to its lytic action.

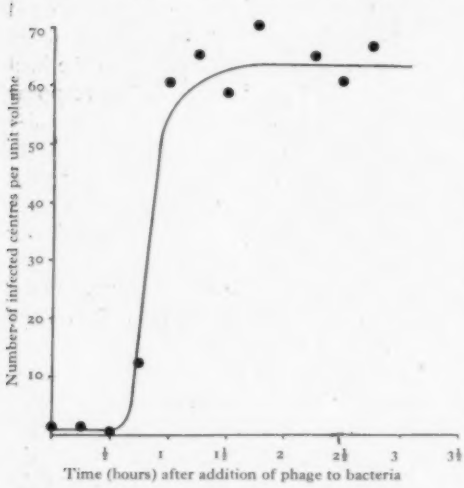


FIG. 2.—'One-step' growth curve of *Ps. æruginosa* phage with latent period of approximately 35 minutes and a burst size of 65. Experimental results have been adjusted to show the yield per single infected bacterial cell. The term 'infective centres' includes phage-infected bacteria of the latent period and free phage particles which are released with the onset of lysis.

Recent studies, and particularly those of Lwoff and his co-workers (Lwoff, 1953) and of Boyd (1951, 1954), have revealed that in such lysogenic cultures all cells contain phage precursor probably in intimate association with the genetic material of the host. Whilst in the majority of cells in the culture the virus remains in a latent form, this mutual adjustment is upset in an occasional cell resulting in the activation of the precursor, multiplication of phage and lysis of the cell. The small amount of free phage thus produced is inactive against the remaining cells of the culture—all of which already carry that phage in latent form—and it can only be detected by a sensitive indicator strain of bacteria. This carefully balanced relationship between host and phage precursor can be upset by exposure to physical or chemical stimuli, e.g. ultra-violet light.

It has been suggested that the phage precursor present in such lysogenic strains actually occupies a position on the chromosomes of the host, and is transmitted to successive generations of bacterial cells in the same way as

the genetic material which controls the specific characters of the host. Induction of phage precursor by ultra-violet light into active phage would then indicate the transformation of a controlled genetic constituent of a chromosome into an uncontrolled entity which fatally misdirects the host's metabolism. That the phage precursor is situated in close relationship to the genes of its lysogenic host gains support from the phenomenon of transduction described by Zinder and Lederberg (1952). These authors have shown that filterable agents, presumably phages from certain Salmonella cultures, can transfer to other members of the same bacterial species genetically controlled characters from their original hosts. Presumably in such instances bacterial genes have been incorporated in the phage during its maturation from its precursor stage.

ANIMAL VIRUSES

In studying the multiplication cycle and constitution of the majority of the animal viruses greater technical difficulties are encountered than is the case with others. The influenza virus is probably the most notable exception. In the first place it can be readily cultivated in the chick embryo and particularly its extra-embryonic membranes; under appropriate conditions it will multiply in the cells lining the allantoic cavity and its progeny be released in large amounts into the allantoic fluid. The virus will even multiply in the parietal layer of the chorioallantois lining the shells of eggs from which the rest of the embryo has been removed and replaced by a simple balanced salt solution (Bernkopf, 1950). Such de-embryonated eggs have proved very useful in the study of a variety of fundamental problems in connexion with influenza.

Secondly, the influenza virus possesses the power of causing agglutination of red blood corpuscles (Hirst, 1941, 1942). This property depends upon the ability of the virus to combine with specific mucopolysaccharide receptors on the surface of the cells (fig. 3), thereby forming bridges attaching adjacent cells to one another. Simple adsorption is not the only action on the red cell, however; by enzymic action the virus will gradually destroy the red-cell receptors and eventually release itself, leaving the red cell no longer agglutinable by that particular strain of virus. Receptors similar to those acting as virus receptors on the red cell are encountered in a variety of mucopolysaccharides occurring in the human and animal body. When present in a virus-red-cell mixture, such substances will inhibit hæmagglutination (Burnet, 1948). By heating under appropriate conditions the influenza virus can be rendered non-infective and enzymically inactive, while still retaining its hæmagglutinating property. Such heated virus is particularly sensitive to soluble inhibitors of hæmagglutination (Francis, 1947) and is therefore often referred to as indicator virus.

By careful study of the hæmagglutination phenomenon various workers (notably Burnet) have defined a variety of features whereby individual in-

fluenza virus strains can be differentiated. For instance, influenza viruses vary in the speed and efficiency with which they destroy the agglutinability of cells for themselves or other strains, and viruses differ in the conditions they require to transform them into indicator viruses for mucopolysaccharide inhibitors of various origins.

Influenza viruses can also be differentiated serologically. Evidence accumulated in recent years shows that they occur in two or three main groups which are serologically distinct. Within at least one of the main groups there is a wide range of minor but nevertheless significant and antigenic differences which are readily demonstrable by complement-fixation or hæmagglutination-inhibition tests; the latter depending upon the fact that specific antibody will prevent hæmagglutination by the virus.

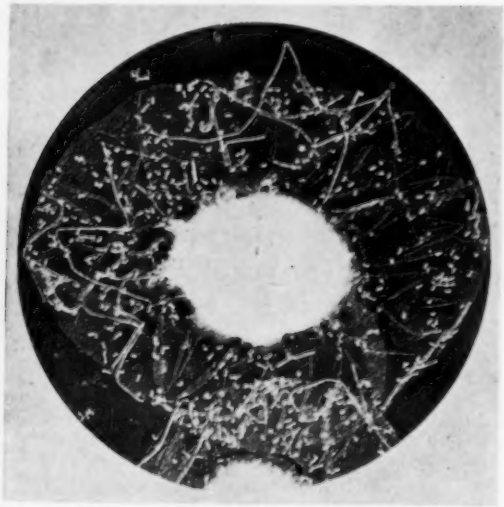


FIG. 3.—Electron microphotograph of influenza virus adsorbed to the surface of laked red blood corpuscles of the fowl. Note the numerous spherical and filamentous virus particles. The large central mass is the nucleus of a red blood corpuscle (× 7,500). (Photograph: National Institute for Medical Research, London.)

In addition to virus, extracts of tissues in which the influenza virus has been cultivated contain another antigen serologically dissimilar to the virus and of much smaller dimensions, but nevertheless demonstrable by complement fixation (Hoyle and Fairbrother, 1937; Henle and Wiener, 1944; Stanley, 1944).

These serological and hæmagglutination phenomena have provided a wide range of traits whereby individual virus strains can be characterized, and they have therefore made possible studies of the influenza viruses along lines similar to those employed with the phages, and which have been briefly referred to above. The results of these studies have revealed that influenza virus multiplication—like that of bacteriophage—goes through a stage of adsorption, followed by a latent period or eclipse phase during which virus is synthesized intracellularly, and finally by the release of active virus progeny from the cells (Henle and Henle, 1949). In the case of influenza, release of the virus progeny is not explosive in its suddenness as with

phages; instead there seems to be a steady release over several hours without recognizable structural abnormality in the parent cells (Henle *et al.*, 1954). The picture of the steps in the process of intracellular multiplication and maturation is still incomplete. It still remains in doubt whether virus particles or groups of major components multiply by repeated binary fission or whether smaller constituents such as individual genes are first produced and from such 'gene pools' virus is finally synthesized, and whether the formation of soluble antigen precedes that of hæmagglutinin which in turn precedes the liberation of the complete or infective virus (Hoyle, 1948, 1949, 1952; Fulton, 1949). There is, however, no reason to doubt why the same fundamental processes are not involved in multiplication of influenza virus as occur in the case of phages.

Further analogies have been revealed by the work of Burnet and his co-workers on recombination (Burnet, 1953). Cells simultaneously infected with two related but nevertheless readily distinguishable strains yield virus which has character derived from both parents.

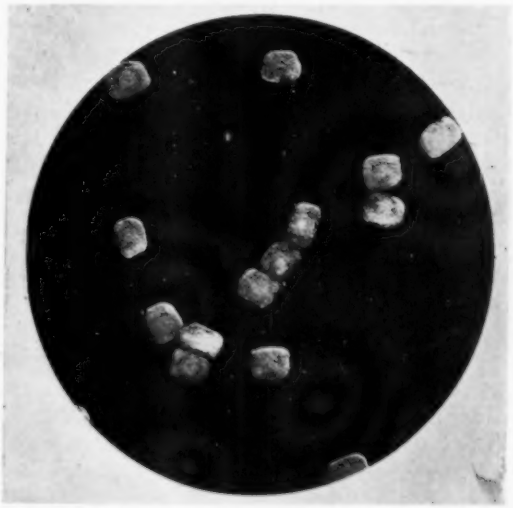


FIG. 4.—Electron microphotograph of vaccinia virus (× 35,500). (Photograph: National Institute for Medical Research, London.)

Many other animal viruses have been studied extensively but, in the absence of such convenient *in vitro* methods as are available for the influenza virus, progress has been less striking; none the less, the findings fit into the same general pattern. The different viruses studied vary in the complexity of their structure: thus, the larger viruses, e.g., that of vaccinia, appear to possess a definite lipoid-containing limiting membrane. Vaccinia virus also shows evidence, detected by electron microscopy, of internal condensation masses, from which a complexity of internal structure can be inferred (fig. 4).

Other viruses appear morphologically less complex than the vaccinia virus, but all, including the smallest viruses known, contain characteristic proteins and nucleic acids. For their multiplication they must find entrance into susceptible cells where their constituents are synthesized during a temporary

eclipse phase which is followed by release of the virus progeny, sometimes apparently without gross structural alteration of the host cells. So constant is the occurrence of the eclipse phase in virus reproduction that it could well be regarded as a fourth criterion in the definition of a virus. In the cells which they parasitize many animal viruses evoke characteristic inclusion bodies for which an analogy can perhaps be found in the polyhedral bodies of insect viruses. Furthermore, many viruses, like that of influenza, stimulate the formation of soluble antigens (Polson *et al.*, 1953, 1954). These need not be virus constituents in a soluble form, but may at least in some cases be the products of cell metabolism altered by the presence of the viruses which, though distinguishable from both virus and host, are nevertheless as characteristic of virus infection as the polyhedral protein is in the case of insect viruses (Bergold, 1953).

It is probably not insignificant, and certainly of great interest, that examples can also be found among the animal viruses of latent infections analogous to those in lysogenic bacteria. Only the classical example of herpes needs to be quoted: an individual once infected—usually in infancy—by the herpes virus remains infected for life. Once the initial infection has been overcome, the presence of the virus remains unnoticed by the victim except when perhaps a febrile illness or an exposure to sunlight upsets the balance between the virus and the host cell it occupies and a crop of fever blisters results.

SUMMING UP

Although much of the evidence is still fragmentary—particularly in the animal virus field—it can be stated justifiably that a clearer picture of the virus is emerging. The picture is fundamentally the same whether the virus is one affecting bacterium or animal. Perhaps the most striking thing is the fact that the picture sketched in broad outline by the bacteriologist is being completed by the biochemist, the physicist and the geneticist.

Instead of visualizing viruses as miniature bacteria, it is becoming more appropriate to regard them as relatively complex chemical structures, sometimes possessing unique morphological features, in which the essential constituents are protein and nucleic acid. Probably only the latter substance endows viruses with their specific activity, whilst the remaining constituents are but components necessary during their extracellular existence. The specific 'reproductive' activity appears to depend upon an affinity for the genetic structures of the host into which they can fit, sometimes more or less permanently, producing little harm, although the majority of pathogenic viruses upset the whole control of normal synthesis by their presence in the cells they occupy.

Thus, in the case of the phage-host relationship in lysogenic bacteria, or in adult insects infected with polyhedral virus, or in the herpes-infected human being, the presence of the virus remains unnoticed in most in-

dividuals until the mutual relationship is disturbed by some external stimulus.

It has even been suggested that in the vast majority of human beings a variety of cancer viruses has similarly become established, remaining entirely latent except in the few unfortunate individuals in whom additional factors have resulted in a disturbance of this balance. Virulent phages and viruses that elicit acute diseases in man and animals also depend for their action upon their affinity for the genetic apparatus of the invaded cells; but here—perhaps by the misdirection of master enzymes—they create havoc in the normal synthetic processes, so that the cell is forced to produce virus protein and virus nucleic acid, sometimes together with certain characteristic by-products as much foreign to it as the virus. The virus has in fact acted as a stimulus for the cell to use its own energy-giving reactions for syntheses which eventually result in its own destruction.

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THE IMMUNOLOGICAL PROBLEM OF INFLUENZA

By C. H. ANDREWES, M.D., F.R.C.P., F.R.S.
National Institute for Medical Research, London

INFLUENZA is a virus infection which tends to attack Britain and other countries in the form of epidemics, roughly every other winter. Adults are affected equally with children. Another virus infection is measles, and this also occurs in epidemics which are greatest every other year; but in this case children are commonly, adults rarely, affected. There are two probable reasons for this difference. The first attack of both viruses is probably upon the respiratory mucous membranes but, whilst influenza infection mainly concerns mucous surfaces, measles only obtains its first foothold there and goes on to reach the blood stream and cause generalized infection. Both viruses give rise to neutralizing antibody. That against measles, even if it cannot prevent the entry of the virus at a second exposure, is placed aright to stop the virus as soon as it dares penetrate to the blood stream. Antibody against influenza, on the other hand, is almost useless while in the blood stream, where there is no virus for it to counteract; and it only imperfectly penetrates to the outside surface of the respiratory mucosa where it is really wanted. Hence its relative inefficiency.

There is, however, yet another reason why influenza can infect adults not once but many times. Unlike measles, which is, so far as we know, antigenically stable, influenza viruses are antigenically unstable. A 'continually emerging antigenic novelty' from one epidemic to another permits successful attack by next year's virus upon people who are resistant to the 'flu viruses of last year and years still farther back. Burnet has called the phenomenon antigenic drift, an idea illustrated in fig. 1. Different antigenic components are shaded differently and a progressive change, or drift, is shown diagrammatically in the composition of strains from successive epidemics. These antigenic changes will be discussed from the point of view of their bearing on the epidemiology of influenza and on the composition of vaccines.

INFLUENZA A, B AND C

Three influenza viruses are known: A, B and C. The more important epidemics are due to A and it is the antigenic changes of A which are most important and have been most studied. 'A' outbreaks affect Britain, and many other countries, roughly every other year; such outbreaks often affect the whole country. 'B' is less important, often causing localized outbreaks, especially in closed institutions such as schools, but rarely affecting the whole country. Influenza B is more obviously an endemic disease than is A; it is liable to turn up here and there in any year. There is evidence of anti-

genic drift as for A, but it seems to be slower and has less obvious bearing on the epidemiological behaviour of the disease. Clinically, an attack of B is indistinguishable from one of A. 'C', the most recently discovered, is probably less important still. Whilst many people have antibodies to it, probably as a result of subclinical infection, evidence that C causes sporadic or epidemic disease in man is scanty. Antigenic changes in virus C have not been described and the infection will not be considered further. Viruses A and B (and probably C) do not engender immunity against each other.

NATURE OF ANTIGENIC DIFFERENCES AMONGST INFLUENZA VIRUSES

For the diagnosis of infection—whether due to A, B, or neither—the complement-fixation test against 'soluble antigen' is a sure stand-by; it takes no note of minor antigenic differences among strains. To detect these,

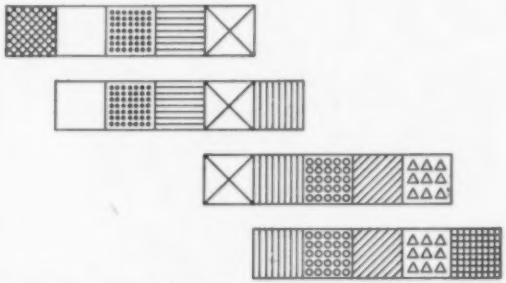

FIG. 1.—Diagrammatic representation of 'antigenic drift' in influenza viruses of successive epidemics (see text).

as is necessary for epidemiological and other studies, the hæmagglutinin-inhibition test is used. Influenza viruses can be grown readily in the allantoic cavity of fertile eggs; these fluids, when they contain virus in high titre, agglutinate red blood cells of fowls and other species. The hæmagglutination is specifically inhibited by appropriate sera, whether of man or immunized or infected animals: our studies have mostly used sera of infected ferrets. By the degree of cross-reaction in these tests, one can tell whether two viruses are closely or remotely related. Figures 2, 3 and 4 give examples of tests showing the antihæmagglutinin titres when we are comparing (fig. 2) two wholly distinct viruses (A and B), two widely divergent strains of A (fig. 3) and two closely related strains of A (fig. 4).

Still deeper insight into antigenic relationships has been obtained by using antibody absorption tests, and several different techniques for applying these to influenza viruses have been described lately. Virus fixed on to the surfaces of red cells is very effective as an absorbing agent (Francis and Jensen, 1953; Fiset and Donald, 1953). Such studies indicate that influenza A viruses may contain a common, relatively unvarying, group antigen and specific antigens which may change from year to year. Francis, Davenport

and Hennessy (1953) have shown that as a result of an attack of influenza, people develop antibodies against the current strain and also receive a boost to antibodies against the strains of which they have had past experience. Thus, sera obtained in a given year, say 1945, will tend to have antibodies against all pre-1945 viruses—or at least those prevalent during the person's lifetime; but such sera will be relatively inactive against post-1945 viruses. One can thus readily see how antigenic instability helps influenza to get about and infect its millions. The degree of change may be slight and many people may remain able to resist a new virus. In some years, however, the change may be considerable, as indicated in fig. 1; such a major change occurred in influenza A viruses in 1946-47. An odd thing is that with the advent of novel viruses, the old ones seem to become extinct. Francis be-

Virus	Serum	
	PR8	Lee
PR8	5120	<10
Lee	<10	480

FIG. 2.—Hæmagglutination inhibition test with PR8. 1934, Virus A. Lee 1940, Virus B.

Virus	Serum	
	PR8	FM1
PR8	5120	30
FM1	<10	960

FIG. 3.—Hæmagglutination inhibition test with PR8. 1934, Virus A. FM1 1947, Virus A.

Virus	Serum	
	FM1	A/Eng/1/51
FM1	1280	560
A/Eng/1/51	160	800

FIG. 4.—Hæmagglutination inhibition tests with FM1. 1947, Virus A. A/Eng/1/51.

lieves that there is a limited range of possible variation in influenza viruses—possibly only eighteen antigens are concerned—and that we shall presently return in a circle to the starting point, having exhausted all the possibilities. Others, however, feel that the future is quite uncertain.

VIRUS CHANGES AND EPIDEMIOLOGY

The changes which occur in influenza A have one favourable feature: they greatly help epidemiological studies by enabling us to trace the doings of influenza viruses all over the world. Influenza A attacks us in Britain roughly every other year; in between it is extremely difficult to detect the virus in Britain at all. Where is it? There are two views. It may be, metaphorically speaking, 'underground', in some latent form where our tests cannot detect it, waiting for the herd immunity to fall or for the occurrence of antigenic change such that it can come out and cause another epidemic. Or else the virus may be travelling around the world all the time, selecting in turn countries ripe for attack. In 1948, the World Health Organization set up the World Influenza Centre with its headquarters at the National Institute for Medical Research, now at Mill Hill, to study this problem and others. It appears from studies here and elsewhere that both views as to influenza epidemiology are probably correct. The virus can persist undetected in a country and become reactivated later: also, when it has done so, an epidemic can spread widely across national frontiers (Andrewes, 1953). This has been

discovered by immunological studies of strains sent to the Centre from laboratories all over the world, studies which are beginning to tell us something of how influenza moves and changes. Happenings in recent years illustrate this.

INFLUENZA 1950-1954

Major winter epidemics are often preceded by small local outbreaks in the preceding summer; these and the subsequent big epidemic have several times been shown to be due to viruses which are antigenically the same. In May 1950, there were local outbreaks in Sweden due to a virus subsequently christened the 'Scandinavian' type. Although, in view of past experience, a good look-out was kept, no virus could be detected during the next three or four months. But in the autumn of 1950, an epidemic due to this virus broke out in Denmark and Sweden, soon spreading to the Netherlands and reaching eastern Britain about Christmas. Only a week or two later fresh outbreaks occurred in Belfast, Glasgow and in Liverpool, where there was particularly high mortality among the old and infirm. These outbreaks were due to an antigenically different virus which was called the 'Liverpool' type. This had occurred widely in South Africa and Australia six months earlier, during the winter of the southern hemisphere. At about the same time as in Liverpool, it afflicted countries along the Mediterranean from Israel to Spain. It soon crossed the Atlantic and affected Canada and the United States. The Liverpool 'wave' thus passed over much of the world.

The winter of 1951-52 was relatively free from 'flu anywhere, but in 1952-53, epidemics occurred again; and over most of Europe, including Britain, Scandinavia, Iceland, Germany and Italy, it was due to a virus very like the 1951 'Scandinavian'. Almost simultaneously there was influenza due to a similar virus in Canada, the United States and Japan. It seemed as though it had persisted in northern Europe and reappeared two years later to cause an outbreak. It could not, however, be argued that this epidemic had spread, as such, quickly over the world, for it appeared almost at the same time in Europe, Asia and North America. If there was a spreading wave, it had done its travelling unobserved, between epidemics (Isaacs and Archetti, 1954).

The Liverpool strain, however, was not yet extinct. It alone was recorded from South Africa and India; and 19 viruses from Portugal were all 'Liverpool'. This virus is more closely related to pre-1950 viruses than is the Scandinavian strain, and it may be regarded as an 'earlier' virus, likely to disappear before we hear the last of the Scandinavian one. Quite recently, Scandinavian viruses have made their first appearance in Australia; and South Africa may yet have a Scandinavian outbreak in store for it.

VIRUS CHANGES AND VACCINES

All these observations are of fascinating interest in relation to epidemiology and may ultimately have great practical importance in teaching us how to

control epidemics. Immunological studies have also a more immediate practical end: that of guidance as to what strains of virus to include in vaccines. Influenza virus grows to high titre in the allantoic cavity of hens' eggs; this virus can be inactivated by formaldehyde and in other ways, and can be concentrated and purified in several ways to give a vaccine of definite value. Trials in the United States in 1943 showed that such a vaccine given under optimal conditions could reduce the incidence of influenza about fourfold. Among the 'optimal conditions' in that trial was the use of a strain in the vaccine which, very fortunately, turned out to be like that causing the outbreak. Trials in 1947, in both Britain and the United States, showed no significant protection as a result of vaccination, doubtless because a major antigenic change occurred in the virus at that time, and the stock vaccine was therefore quite useless. How can we avoid such a fiasco again? It is likely, as might be guessed from fig. 1, that use of the most recent available strain will give fairly good cover against a new one which is not widely different. Occasionally, as between 1945 and 1947, a big change in the virus will occur and then we shall be less fortunate. Now and again, as in 1943, one may pick up and prepare vaccine from a precursor summer outbreak, preceding a big winter one. We also hope that workers at the World Influenza Centre will become better guessers as to what virus strain is likely to trouble any particular country.

If a new strain arises anywhere in the world, it is theoretically possible to isolate virus and send it to another country, to give the manufacturers there time to prepare vaccine from it before their country is hit. In fact, such a thing was proved feasible in the United States in 1951. But in practice it is very difficult to prepare vaccine of known potency and safety on any large scale within a matter of months. Should a lethal pandemic like that of 1918-19 recur, all possible efforts to work swiftly would be called for. With the less terrifying influenza of more recent times, such rush tactics may not be necessary or justifiable.

OTHER ASPECTS OF VACCINATION

It is possible to make influenza vaccines of such potency that they not only give protection but also induce unpleasant local and general reactions. A balance between potency and safety has therefore to be struck. In this country, vaccine adsorbed to aluminium phosphate has proved potent and relatively free from the dangers of troublesome reactions. Recently attempts have been made to use vaccines emulsified with oily adjuvants. Such vaccines certainly produce, for a given amount of virus content, a larger and more durable antibody rise. Since a useful effect can be produced with smaller doses, rapid vaccine production in an emergency would be greatly helped. Unfortunately, we are not yet in a position to say that such vaccines are devoid of the risk of producing late reactions. Fears that the oil in the emulsions will be carcinogenic are probably unjustified; but persistent nodules and even sterile abscesses at sites of inoculation have been reported

too often for complacency; and these may be first observed a year or more after the injection.

The results of influenza vaccine trials have proved very difficult to assess. This is largely because the disease is so hard to diagnose clinically. Febrile catarrh may occur in epidemics and cause confusion (Stuart-Harris *et al.* 1938). It may happen that influenza and febrile catarrh are prevalent at the same time; and if a vaccine has been used, having protective value against only one component of the outbreak, it may well fail to impress. Attempts have been made to assess vaccines by considering only serologically proven influenza cases: but here lies another pitfall, for vaccinated people may show an antibody rise as a result of their vaccination and no further rise if they nevertheless subsequently fall victims to 'flu. Thus, serological diagnosis is apt to be of less than normal value in a vaccinated community. It seems that we can only learn the answer as to the value of vaccines when communities under study are later afflicted with an outbreak which is almost pure influenza. Unfortunately it will be difficult to reach finality, for if the viruses are always changing, so must the vaccines, and viruses from different outbreaks may differ in their potency as immunizing agents.

CONCLUSION

The possibility of recurrence of a lethal pandemic like that of 1918-19 is a main justification for developing vaccines. Their practicability for 'ordinary' influenza is questionable. Long-lasting immunity to a given strain will be hard to achieve and is doubtfully worth while if that strain has a limited expectation of survival. To control influenza by vaccination one thus has to contemplate vaccinating millions of people every other year, and such a proposition is doubtfully worth while on purely economic grounds. It may be best to have available the best possible vaccine for people in key positions, especially important for the welfare of the community, and for others, particularly vulnerable, who may demand it. It will then be best to give it in November or December, before an expected outbreak: incidence of outbreaks has been roughly every other year, usually in January, so a guess will be right more often than not. On such a basis influenza may be expected this winter. Patients who ask for vaccine on the grounds that they have a terrible attack of influenza every winter can safely be told that whatever they have every winter is pretty sure not to be virus influenza.

The matters discussed in this article are dealt with in more detail in 'Influenza. A review of current research': No. 20 in the World Health Organization's Monograph Series, Geneva, 1954.

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POLIOMYELITIS PROPHYLAXIS

By W. H. BRADLEY, D.M., M.R.C.P.
Senior Medical Officer, Ministry of Health

THERE is general agreement that the main hope of preventing poliomyelitis is by artificial immunization.

About 20 years ago two vaccines were tried in the United States. In one (Kolmer) it was believed that the addition of ricinoleate had attenuated the virus to a safe level. In the other (Brodie) formalin was used to inactivate the virus. Although several thousand individuals were inoculated the prophylaxis efficacy was not assessed in man, largely because of the inherent difficulties in such trials, and the occurrence of a dozen cases of paralytic poliomyelitis with high fatality six to fourteen days after the inoculation led the medical director of the U.S.P.H. Service to issue a warning against the use of these vaccines (Leake, 1935). Leake's report mentions that 'in every case in which the sequence is known the level of the spinal cord first affected corresponded to the extremity in which the infection was made, paralysis beginning either in the same limb or the contralateral limb'. In 1950 it was observed that paralysis, often limited to the inoculated limb, followed the inoculation of other vaccines, and it is now amply confirmed that the injection of certain non-specific antigenic and chemical substances may precipitate poliomyelitis. Thus, the accidents reported by Leake may have been due either to imperfect attenuation or inactivation of the poliomyelitis virus or to less specific causes, and both possibilities cast a shadow over active immunization.

A new phase in the study of poliomyelitis began in 1951 when Enders *et al.* (1952) introduced a successful method of cultivating poliomyelitis virus on tissue culture which, incidentally, made the mass production of vaccines possible. With commendable courage the United States National Foundation for Poliomyelitis has hastened to promote a vast trial of an inactivated vaccine. This trial is now being watched by the United States Public Health Service and the official result will not be known before the end of this year.

Although convalescent serum has been used many times since the first attempt by Davide in 1925 to prevent poliomyelitis, new hopes of applying it successfully came when Bodian (1952) demonstrated that paralytic poliomyelitis results from a series of consequential stages of multiplication of the virus, first in the pharynx and gut, then in the blood, and then in the central nervous system, and that these three stages can be dissociated by the administration of gamma globulin. Given the tissue culture technique it is now possible to measure this virus-neutralizing effect of serum. In

October 1952, Hammon and his colleagues from Pittsburgh described a plan for controlled field tests which appeared to be justified by a pilot study conducted during 1951 in Utah to evaluate American Red Cross gamma globulin as a prophylactic agent. Together, these trials gave what at first sight appeared to be encouraging results, but unfortunately a vast field trial in 1953 damped any enthusiasm for the use of passive immunization in mass prophylaxis.

These disappointing results with gamma globulin and the uneasiness regarding vaccines must discourage any hope that artificial immunization against poliomyelitis is either at hand or immediately round the corner. This being so, a review of the more general and time-honoured measures ordinarily used in the control of a communicable disease has been included in this article.

GENERAL CONSIDERATIONS

The mechanism of resistance to virus diseases is imperfectly understood. Viruses have been called the 'ultimate parasites of nature' because, in order to survive and multiply, they must find their way into the individual tissue cells which are damaged or destroyed in the process. The humoral antibodies would seem to be available only to impede the entry of the virus into the cell. This suggests that there may also be some unknown mechanism of tissue immunity.

Be this as it may, the effectiveness of active immunization in prophylaxis against some virus diseases has been proved to the hilt, and this long before viruses themselves were thought of. Lady Mary Wortley Montagu introduced variolation into England from Turkey in 1717, and the success of this method was, almost certainly, one of the causes which led Jenner to investigate cowpox in the prevention of smallpox. The principle behind Jennerian vaccination is now widely applied. Cox (1954) lists 13 different virus agents employed as living attenuated vaccines in the practice of human or veterinary medicine. In general, killed or inactivated virus is a relatively poor antigen compared with the living virus as used in smallpox vaccination and yellow fever immunization. Although Jenner's approach was empirical he, in fact, selected a variant from the vaccinia-variola group of viruses which is almost exclusively dermatotopic and yet which protects against the most severe form of smallpox. In yellow fever immunization a living attenuated strain of pantropic virus (17D) is used. The immunity produced by both these vaccines endures at a useful level for ten years or more in the great majority of persons immunized.

Thus, there is no theoretical reason why an attenuated live poliomyelitis vaccine should not be equally effective and enduring. Because the immunity from killed vaccines is shorter in duration and because poliomyelitis virus is peculiarly resistant to some forms of chemical treatment (WHO, 1954), there are *prima facie* reasons for choosing the Jennerian approach.

T. E. Boyd (1953) points out that previous attempts at immunization

against poliomyelitis were largely vitiated by unrecognized sources of error, the most serious among which were:—

(a) Lack of quantitative methods for assaying viruses and antiserum.
(b) Ignorance of immunological diversity among poliomyelitis viruses.
(c) Use of inappropriate animal species and routes of inoculation for testing the resistance to infection conferred by immunizing procedure.

He reviews recent advances in knowledge and concludes that in animals the protection afforded by passive immunization is brief and that with active immunization it lasts for a still undetermined but more substantial period of time. He also discusses existing methods of assaying viruses, antisera and vaccines so that the dosage can be controlled and the usual safeguards, such as those required by the Therapeutic Substances Act, can be applied.

THE ANTIGENS

Three immunologically distinct types of poliomyelitis virus are known. These are also distinguishable by other peculiarities, such as host range and their behaviour on tissue culture and in transmission through animals. Type 1 is called 'Brunhilde', type 2 'Lansing', and type 3 'Leon'. Both types 1 and 3 produced outbreaks in the United Kingdom during 1952 and 1953. So far, type 2 has not been found responsible for an outbreak in this country but has been recovered from several sporadic, including fatal, cases.

There are strain differences within the antigenic type and it has been suggested that these are associated with differences in severity observed in experimental animals and also in comparisons between outbreaks, but the evidence is still slender. Experimentally, the behaviour of these strains can be modified by adaptation and passage in animals, but there is no evidence of sudden mutation in man. The three known types were identified because they are pathogenic to monkeys. Since the tissue culture method for growing poliomyelitis virus was introduced the existence of still other types of virus-producing disease in man but not in monkeys has been suspected (Duncan *et al.*, 1954).

ANTIBODIES

Neutralizing and complement-fixing antibodies occur in the blood of patients suffering from poliomyelitis: they decline with the passage of time. Regarding the three known types, the report of the WHO Expert Committee (1954) says:

'It is clear from experimental data that immunity to one type of virus does not furnish protection against the other two although in human populations antibodies of type 2 virus may indicate the probability that previous experience with another type has occurred. . . . There is divergence of opinion as to whether durable immunity is acquired from single infection.

'Second paralytic attacks are uncommon: there is insufficient information to determine whether they are caused by the same or by different strains of virus.

'There are as yet insufficient measurements to establish a correlation between

levels of antibody in the blood and the degree of resistance to poliomyelitis virus. It may be difficult to obtain this information, because the variation in response to infection is great among non-immune and the differences are not strictly related to immunological resistance.

'Present data indicate that circulating antibody does not necessarily prevent alimentary infection in man, but it may well serve to interfere with spread of virus to the central nervous system and therefore with a production of paralysis'.

Because type 2 virus is pathogenic to mice, antibodies to it could be studied with ease even before tissue culture methods were available. Neutralization tests on mice are not strictly specific for type 2 but this method has been used for extensive surveys of populations in different parts of the world, and it has appeared that the blood of some primitive races is endowed with the power to neutralize at least some of the poliomyelitis viruses. For example, 90 per cent. of bloods from Australian aborigines in the northern territory, five years old or more, were shown by Miles (1953) to neutralize type 2 virus, this capacity being maintained at a steady level at all ages above five, suggesting constant renewal of antibody by boosting infections. Clinical poliomyelitis has not been recognized among these people. Also, there are no significant differences between groups from different areas in the territory or between groups living under certain conditions with a varying amount of contact with white men. This and the many similar investigations have led to the surmise that poliomyelitis virus might be very widespread, in fact ubiquitous, in some populations and that as a result man has become largely adapted to the virus and disease does not occur. This idea of ubiquitous infection, however, cannot always be applied, because other primitive people do not carry the same neutralizing factor in their blood in the absence of overt disease. The most striking example is recorded by Paul and Raordan (1950) who studied Eskimo communities which had been free from poliomyelitis for twenty years. Only serum from persons over twenty years of age contained a neutralizing factor which might well have been associated with a past epidemic. It was in such circumstances that the serious 'chain' outbreaks at Chesterfield, Hudson Bay, described by Moody and Adamson (1949), occurred. In a population of 275 Eskimos, 51 developed paralysis and 14 died.

These two instances reveal two situations: in the case of the Australian aborigines the freedom from disease might be attributed to the ubiquity of antigens (although the presence of a disease-producing virus or any other poliomyelitis antigens has not actually been demonstrated), but in the case of the Eskimos the absence of antigen, in the Chesterfield community for as long as forty years, seems to have been their salvation.

It can be assumed that, when a disease-producing poliomyelitis virus is present in a community, variation in individual resistance and susceptibility is due to both specific and non-specific host factors and we do not know which is the more important. Furthermore, the level of antibody in the blood has still to be correlated with resistance to the disease. The answers to these

questions will be obtained only by clinical and field investigations. Animal experimentation, which has been extensive (Boyd, 1953), is unlikely to carry us much further.

There are three approaches to the artificial production of antibody: by killed virus parenterally, by active virus of low virulence under cover of antibody, and by live avirulent virus given either orally or parenterally.

Regarding passive immunization, since man is almost certainly the only natural host of poliomyelitis virus and, apart from certain monkeys and chimpanzees, other vertebrates are insusceptible, it seems that man is the only source of antibody, the supply of which is therefore always going to be difficult. Pooled human gamma globulin is, however, known to neutralize the virus both *in vitro* and *in vivo*, and a place for its rational use, on a limited scale, in prophylaxis may still be found.

ACTIVE IMMUNIZATION WITH KILLED VIRUS

At the beginning of 1953 it was announced that American agencies would spend $7,500,000 on a formalin-inactivated vaccine incorporated in a water-in-oil emulsion. The plan was to test this in first, second and third grade schoolchildren in nearly 200 chosen test areas starting in the southern states in April and progressing northwards, keeping ahead, as it were, of the beginning of the poliomyelitis season. It seems that some 650,000 children in the second school grade (ages 6 to 8 years) received injections anticipating the poliomyelitis season of 1954: 40 per cent. of these children were not in a strictly controlled trial. Of the other 60 per cent., half were given vaccine and half saline, thus providing a 'placebo controlled group'. When Salk (1953) described the preliminary experiment which led to the use of the vaccine now under trial in the United States, he showed reasons for believing that it should be possible with non-infectious preparations to approximate the immunological effect induced by the disease process itself, but he added:—

> 'Although the results obtained in these studies can be regarded as encouraging they should not be interpreted to indicate that a practical vaccine is now at hand. . . . Because of the great importance of safety factors in studies of this kind it must be remembered that considerable time is required for the preparation and study of each new batch of experimental vaccine before human inoculations can be considered. . . . It is this consideration, above all else, that imposes a limitation in the speed with which this work can be extended'.

The American trials are proceeding against this background. They are purely experimental and it is hoped that they are so well controlled that there will be no need to repeat them in this country. If they succeed it does not mean that the ideal vaccine has been found. Up to the end of August 1954 there has been no mention of ill-effects.

COMBINED ACTIVE AND PASSIVE IMMUNIZATION

The data available on serum-virus mixtures indicates that such have, at best, a feeble antigenic effect compared with that of virus alone or with

that of virus and serum given separately. Bodian (1951) obtained relatively small rises in antibody titre when virus and gamma globulin were administered independently but simultaneously. Antibody declined to barely detectable levels in three weeks but it is also clear from a more recent article (Bodian, 1953) that the administration of gamma globulin does not interfere with the acquirement of inapparent intestinal infection or with the development of active immunity when the virus is fed to monkeys (and the gamma globulin, of course, given parenterally), but the tendency towards the latter is certainly depressed by the antibody. Hammon *et al.* (1952b) and others have observed that alimentary infection may occur without evoking active response in the form of circulating antibody and that when antibody is already present a new alimentary infection may not cause further active response.

Combined active-passive immunization does not appear to have been tried in man. On the face of it, feeding virus under cover of parenteral injections of gamma globulin is unlikely to be effective under conditions of mass immunization.

LIVE VACCINE

Sabin (1953) and Cox (1954) and several other authorities have stated a strong preference for live vaccine on the grounds that living virus vaccines induce immunity through the same mechanism used by nature—by producing subclinical infection—and that they confer immunity for many years or for life.

Sabin explains that although a certain amount of antigenic overlapping among the three immunological types of poliomyelitis viruses has been revealed by both complement-fixation and neutralization tests, there is no evidence that active infection with one type will provide immunity to the others. It has been repeatedly found that, in patients with high titres of antibody for type 2 virus, poliomyelitis due to type 1 develops. Previous oral infection of cynomogous monkeys with type 2 virus provided no immunity to paralysis resulting from injection of type 1 virus. A live vaccine will therefore have to contain avirulent strains of all known types unless some new strain of unusually broad antigenic composition is found.

The numerous difficulties still to be overcome are reviewed by Sabin and cannot be easily summarized in a short article. He points out that the basic information which one should have about a vaccine before it is tested in human beings is not yet available and that it cannot be available until a suitable reproducible method of assay in experimental animals, not in human beings, has been developed. Whilst Cox believes that a living attenuated virus offers the most logical and hopeful approach towards solving the poliomyelitis problem, he feels strongly that virus should not be propagated in the tissues of mammals because of the difficulties of excluding the presence of other virus or microbic agents infectious to man, and points out the difficulties of assuring adequate purity, safety and identity. He hopes that egg culture of a suitable attenuated virus will provide the solution and has succeeded in adapting the M.E.F.1 strain of Lansing type virus to the chick embryo.

There is another hypothetical difficulty about vaccines, dead or alive, produced on tissue culture, particularly when derived from human sources, which has been referred to as 'organ damage'. Freud found that extracts of testicle inoculated with oily adjuvants and microbacteria can lead to degeneration of the testicle in the recipient. Obviously, it is essential that vaccine should be devoid of substances likely to produce undesirable side-effects such as this and anaphylaxis and the more remote hypothetical results, such as carcinogenesis, which might follow the use of certain adjuvants.

The greatest difficulty with a live vaccine is to decide when the virus used is in fact non-pathogenic. The search for spontaneously occurring or experimentally developed avirulent strains calls for fundamental knowledge of the conditions which favour the appearance and segregation of variant or mutant as well as the properties by which they can be characterized. Although a great deal of fundamental work in this direction is in progress the results must be checked and re-checked.

For example, as long ago as 1941, Theiler reported that after 50 rapid intracerebral passages in mice, the Lansing strain of poliomyelitis virus no longer produced signs of poliomyelitis in eight Rhesus monkeys inoculated intracerebrally. More recently, Bodian *et al.* (1950) and Melnick (1951), when checking this result, found that the same strain of virus still produced paralytic poliomyelitis in Rhesus monkeys after approximately 200 or more intracerebral passages in mice. Other strains of poliomyelitis have lost much, although not all, of their paralyticogenic activity in monkeys after passage in mice, rats or hamsters. At the same time they have gained in virulence for a new host. Type 1 (Brunhilde) virus when passaged in tissue culture on human non-nervous tissue tends to lose its paralyticogenic activity in monkeys: unfortunately, only by a trial on humans could we discover whether this form of tissue had caused it to acquire greater virulence for man.

In fact it seems that the search for the ideal avirulent strain of poliomyelitis virus may prove a long and complicated task. In the meantime, Koprowski (1954) has fed a polyvalent living virus vaccine to several score of children and has established intestinal carriage in nearly half of them without paralysis resulting. In some cases a satisfactory antibody response has lasted for four years.

PASSIVE IMMUNIZATION

Convalescent human serum was first tried in the prophylaxis of poliomyelitis during an outbreak in Northern Sweden in 1925 (Davide, 1928) and there have been many attempts since, terminating in a series of trials organized by Hammon and his colleagues (1952a) from Pittsburg. A pilot study to evaluate American Red Cross gamma globulin began during 1951 in Utah, where 5,767 children were injected with either gamma globulin or gelatin during a poliomyelitis epidemic, but the number of cases of poliomyelitis occurring in the injected group was too small to give a result. In 1952, 33,137 children aged from 1 to 6 years were injected in Texas and 15,686 children between 2 and 11 years of age in Nebraska. Ninety cases of poliomyelitis were observed in these two groups, 68 being among children receiving gelatin as a control and 26 in the comparable gamma globulin

group. After the eighth week morbidity from poliomyelitis was the same in both groups, but before the eighth week the incidence was as follows:—

Weeks	Gelatin group	Gamma globulin group
1	16	12
2-5	39	7
6-8	13	7

On this evidence the Department of Federal Security and the National Foundation against Poliomyelitis in America combined to marshal as much gamma globulin as possible so that during 1953 extensive trials of prophylaxis by this method could be attempted. The results were summarized by the U.S. Committee for Gamma Globulin (1954). Altogether the Health Departments in 41 states and four cities collaborated. Detailed epidemiological descriptions were collected in each of the 23 areas where mass inoculation was given to 235,000 children. In five of these areas the incidence of disease after the mass immunization was sufficiently great to warrant assigning a physiotherapist to measure the possible modifying effects of the gamma globulin on the clinical state. In other areas, where mass immunization was not applied, the household contacts in selected cases were given gamma globulin and the results controlled by observation on 'matched households'. Multiple cases of poliomyelitis occurred in 749 of these households, involving 1,654 individuals.

Although the most elaborate preparations were made for assessment, it was never easy, and in many instances impossible, to arrive at any evaluation in the mass immunization studies, and nowhere did the trials yield statistically measurable results. The Committee concluded that the value of gamma globulin in community prophylaxis had not been demonstrated. On the other hand, the data derived regarding the efficacy of gamma globulin in the protection of household contacts were considered to be adequate for reliable conclusions and indicated that, in the doses used, there was no significant effect on: (1) the severity of paralysis developed in any subsequent cases, (2) the proportion of non-paralytic poliomyelitis occurring in subsequent cases, (3) the classic pattern of familial aggregation of cases.

Hammon himself added a minority comment to this report alleging that the gamma globulin had been given too late to have any consistent effect and pointed out that he had already predicted that passive immunization had an extremely limited application in the field of preventive medicine.

In the background of this great investigation was what the *New York Times* of March 14, 1954, referred to as 'misunderstanding and confusion'. An editorial in the *New England Journal of Medicine* (1954) says that this was brought about by radio voices that trumpeted the precious protein during the campaign for funds as though it were almost a cure and, at least, a satisfactory preventive for poliomyelitis. It also mentions that 19 million dollars of the public's money is being spent on the 1954 gamma globulin programme of the National Foundation for Infantile Paralysis

and comments 'there should be little ground for continued enthusiasm for this method of bleeding part of the population for the dubious objective of postponing poliomyelitis in other parts for a month or two and at the cost of about 25 thousand dollars for each possible case postponed'.

It is interesting that the apparent success of the first trial may have been due to the disproportionate occurrence of paralysis precipitated by the gelatin given to the 'control group' and illustrates a difficulty already mentioned. Clearly, a great deal more study will be necessary before the last word is said about passive immunization and recently, at the 3rd International Poliomyelitis Congress in Rome, Hammon, reviewing the diagnostic, and Muench the statistical, criteria, concluded that gamma globulin had, in fact, done some good. The poor result of this 1953 trial may have been due to insufficient dosage, which raises a serious difficulty because gamma globulin is in short supply in America as everywhere else. A crucial problem is the need to develop techniques for predicting how poliomyelitis will behave in a given country or community. Opinions will continue to differ regarding the need for gamma globulin in special circumstances but a recent memorandum from the Ministry of Health (1954) has defined the situations in which we are permitted to use our limited supplies which, incidentally, are as potent as the product of American blood (Heald, 1954).

EPIDEMIOLOGICAL ASPECTS OF IMMUNIZATION AGAINST POLIOMYELITIS

Even when the tools for artificial immunization become available there is still doubt regarding the place of immunization in the control of poliomyelitis and further experiments in the field will also be necessary to discover how immunization can best be used. Paralysis is an almost accidental and unpredictable occurrence in the course of a systemic infection which in itself is of little importance. Certain immunological studies have been interpreted to indicate that the infection is almost ubiquitous, particularly in primitive people, and that natural immunity is acquired by the majority of individuals very early in life. Field observations, particularly in this country (Bradley, 1954), and virological investigations by Francis (1952) in the United States have led to the conclusion that, under the conditions of western civilization at least, there is a limited selective distribution of disease-producing virus and that the more general pattern revealed by immunological study may not be the one upon which plans for immunization can be based, particularly if the resulting protection is short-lived.

About one-third of the cases of poliomyelitis notified in the United Kingdom fall into each of the three age-groups, 0-4, 5-14, and 15 and over, and even with a live vaccine, which at best would give an immunity enduring for, say, ten years, the problem of how best to use boosting doses will be considerable. There is one useful indication, however. It seems clear that in infants the paralysis itself tends to be relatively mild and the severity and mortality increase as age progresses. Sabin (1953) studied this

phenomenon in mice and found that immunity without concomitant paralysis is acquired most easily in early life.

GENERAL MEASURE OF CONTROL

The report of the WHO Expert Committee on Poliomyelitis says:—

'The accumulated laboratory and epidemiological evidence indicates that poliomyelitis is a highly infectious disease spread by intimate association with infected persons. It is probable that the virus is actually transferred directly or indirectly by means of pharyngeal excretions and fæcal matter.

'The standard methods of control as applied by health officers with many infectious diseases have been found to be of little avail in poliomyelitis. Part of the reason for the apparent failure of isolation and quarantine measures to check the spread of infection may lie in the fact that for every case of paralysis there may be a large number of persons with mild or inapparent infection. However, virus studies have shown that, during epidemic periods, virus is found mainly in the intimate associates of the case. It appears possible therefore that some reduction in the number of cases of poliomyelitis might be achieved by vigorous quarantine and hygiene measures directed at the first recognized case.

'Because of prolonged excretion of virus in the stools, it is probably advisable that patients should be isolated, if necessary at home, but it is difficult to make a firm recommendation as to the length of time because it is not known when the individual case becomes free from infection. There would appear to be much to commend the practice in some countries of isolating cases and quarantining contacts for three weeks'.

This opinion, which may come as a surprise to some, is in line with the policy advocated in a series of memoranda issued by the Ministry of Health, in 1936, 1947 and, the last, in July 1954. Although there are no powers to enforce 'vigorous quarantine' in the United Kingdom, it is advised that a drill no less energetic than that used for the control of smallpox should be applied. This involves the instruction and some degree of surveillance of the close contacts and depends upon the thoroughness with which contacts are ascertained. Such a drill, concentrating on affected households and the contacts, is deemed to reduce the need for action by the population at large who can be reassured that everything possible is being done to contain the infection.

Special attention is directed to the one prophylactic measure about which there is no doubt: the discontinuance of tonsillectomy and inoculations when there is reason to believe that paralysing virus is in the neighbourhood.

SUMMARY

This review was completed after the Third International Conference on Poliomyelitis held in September 1954 at Rome and includes views expressed there.

Although artificial immunization offers the best hope of preventing poliomyelitis the necessary tools are not yet to hand. The great trials undertaken in the United States both of passive immunization with gamma globulin and of an inactivated virus vaccine (Salk) are entirely experimental. Although 'no significant effects' were observed by the U.S. Committee for Gamma

Globulin there is still hope that a place for passive immunization will be found. Regarding the 'Salk' killed vaccine, the first statement of results will not appear before 1955. If they are encouraging time alone will discover whether permanent immunity can be obtained without too frequent boosting. Unfortunately there is as yet no way of correlating the level of antibody in the blood with the degrees of resistance to infection and paralysis.

Theoretically, killed virus vaccines are not expected to provide enduring protection and, mainly for this reason, the objective is an attenuated live vaccine administered either parenterally or by the oral routes.

The search for an effective and trouble-free vaccine suitable for mass immunization is likely to be protracted and must proceed through a series of field trials. In the meantime, attention is called to a change in views regarding the epidemiology of poliomyelitis. It is now more generally accepted that there is a 'limited selective distribution' of disease-producing virus which is concentrated in the vicinity of the patient in the acute phase of the disease and his contacts, and routine measures as advocated in a recent Ministry of Health memorandum are commended.

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THE IMPORTANCE OF COXSACKIE VIRUSES

By EDWARD A. BEEMAN, M.D.

(Formerly) Viral and Rickettsial Section, Laboratory of Infectious Diseases, National Microbiological Institute, Bethesda, Maryland

'COXSACKIE VIRUS' is an inclusive term applied to a newly recognized class of human pathogens comprising at least two heterogeneous groups of viruses. The initial strains were recovered from two patients with paralytic poliomyelitis in Coxsackie, New York, and they were first described by Dalldorf and Sickles in 1948. These agents have been grouped together chiefly because of their ability to produce characteristic lethal illnesses in suckling mice and hamsters. Dalldorf discovered them accidentally while seeking new laboratory hosts for the propagation of poliomyelitis virus. Not unnaturally, the Coxsackie viruses were sought for among patients with poliomyelitis or poliomyelitis-like syndromes during the early phases of their investigation. The ubiquity of these viruses, especially in the summer months among children, their capacity to produce widespread inapparent infections, and their persistence in stools for long periods of time resulted in their isolation from, and association with, many cases of poliomyelitis. Various investigators were led to speculate that the Coxsackie viruses might have some relationship to the etiology of poliomyelitis. Subsequent epidemiological and clinical studies have failed to support these hypotheses. Continued work on and interest in the nature of these agents have gradually resulted in a clearer understanding of the role that they have assumed in the causation of human illness. Evidence at the present time suggests that the main diseases produced by Coxsackie viruses are herpangina and epidemic pleurodynia.

PROPERTIES OF THE VIRUSES

The immunological specificity of many of the available strains has been determined adequately. Table 1 presents a tabulation of 16 serological district types of Coxsackie viruses and their designations as recorded by the various laboratories where they have been isolated or investigated. Several other serological types are known to exist and new serological types are constantly being added to the strains already known. Dalldorf first indicated certain marked pathological differences produced by these viruses in suckling mice and on this basis has proposed further segregation of them into groups A and B.

Table 2 presents some of the attributes and distinguishing features of the two groups. Group A viruses, which include 10 or more serologically distinct types, characteristically produce extensive liquefaction necrosis of skeletal muscle and virtually no other observable pathological findings in suckling mice and hamsters.

These species after their first two to three weeks of life cannot be infected by group A viruses. Except for a few strains that produce muscle necrosis in chick embryos, group A viruses are known to infect only the chimpanzee which exhibits no more than an intestinal carrier state followed by an immune response. Tissue cultures may be used to propagate some strains. The group B viruses were originally so classified when Dalldorf found that they produce only mild to moderate focal muscle lesions while also causing a characteristic encephalopathy and panniculitis.

Albany (Dalldorf)	New Haven (Melnick)	Washington, D.C. (Huebner)	Other
	Group A		
Types 1	Easton 2 (Type 1)	Type 1	B-J*
2	Type 2	Type 2	
3	Type 3		
4	Texas 1, High Point	Type 4	Minn. SY1, SY2** Dallas, M.B.*
5	Easton 14	H1	
6	Israel 7	H4	
7	Texas 15		
8	Easton 10	H2	
9	Boston		
10	Alaska 5	H3	
	Group B		
Types 1	Connecticut No. 5		Demole, Kine†
2	Ohio 1		
3	Nancy	Texas Pleurodynia	Washington 518‡
4	Texas 13		Powers§
	Unclassified by Group (New strains continually being discovered)		
	Texas 12		
	Texas 14		
			Matulaitis§

TABLE 1.—Classification of serological types of Coxsackie viruses described in the literature, and their designation in various laboratories.

*Sulkin, S. E., *et al.* (1950): *Proc. Soc. Exp. Biol. (N.Y.)*, **73**, 340.
Slater, E. A., and Syverton, J. T. (1950): *Ibid.*, **74, 509.
†Weller, T. H., *et al.* (1950): *J. Immunol.*, **65**, 337.
‡Lazarus, A. S., *et al.* (1952): *Amer. J. publ. Hlth*, **42**, 20.
§Cheever, F. S., *et al.* (1950): *J. exp. Med.*, **92**, 153.

Additional work by others showed that certain strains classified by Dalldorf as belonging in group B produced extensive pancreatitis as well as other visceral lesions in both suckling and adult mice.

The Dalldorf grouping has been adopted as a useful working classification by several investigators. Huebner and his co-workers feel that this separation of Coxsackie viruses into two distinct groups is further justified by controlled epidemiological studies of their behaviour in their only known natural host—man.

All the Coxsackie viruses appear to be extremely small, exhibiting a size range commonly accepted also for the viruses of poliomyelitis and murine encephalomyelitis.

Several of the agents have been obtained in a highly purified concentrated state and have been visualized in the electron microscope. One group A strain grown both in suckling mice and in chick embryos yielded identical particles from both. The

Attribute	Group A	Group B
Laboratory host range	Suckling mice, suckling hamsters, chimpanzees, chick embryos (several serological types). Tissue culture: human and mouse tissue.	Same as for Group A. In addition adult mice and Cynomogous monkeys.
Illness in suckling mice	Generalized involvement of all skeletal muscle groups resulting in flaccid paralysis and death. (Type 1: stiffness and paralysis of limbs, characteristic wrist drop, asymmetrical contracture deformities of torso and limbs, followed by death.)	Larger infectious doses produce short incubation period, ataxia, cyanosis with fine tremors followed by death; smaller doses produce longer incubation period, convulsions, spasticity, followed by death (occasional recovery).
Illness in adult mice	None.	Subclinical infections mostly. Occasionally loss of weight, hunched back, ruffled fur, death.
Pathology		
Suckling mice	Generalized liquefaction necrosis of all skeletal muscles except tongue. (Type 1: more focal muscle necrosis.)	Pancreatitis, encephalomyelitis, myositis, panniculitis, hepatitis, myocarditis.
Adult mice	None.	Pancreatitis, necrosis of acinal cells.
Physical Characteristics		
Resistance to chemical agents:		Diethyl ether, ethanol (70%), lysol (5%), phenol, 'roccal' (1%), dyes, antibiotics.
Inactivated by:		Halogens, formaldehyde (0.3%), hydrochloric acid (0.1 N).
Thermal death point:		51°-60° C. (most, 53°-55° C.).
Size 1. Ultracentrifugation and electron microscope:		25-37 millimicra.
2. Ultrafiltration:		15-23 millimicra.
Shape:		Spherical.
pH viable range:		2.3-9.4.
Preservation:		−20° to −70° C. indefinitely; 50% glycerol or horse serum at room temperature > 70 days; 4° C. > 1 year.

	Herpangina	Epidemic Pleurodynia
Association with human illness:	Types 2, 4, 5, 6, 8, 10 (possibly type 3 and others).	Types 1 and 3 (probably type 4 and possibly type 2).
Strains for which specific disease undetermined:	Types 1, 3, 7, 9. (Ungrouped Texas 12, Texas 14, Matulaitis).	Types 2 and 4.

TABLE 2.—Current knowledge of some attributes of the Coxsackie viruses.

particles of group A and group B strains, which have been visualized, are remarkably similar and no difference in size could be determined either by electron microscopy or by ultracentrifugation studies. Calculations from electron microscope images gave an average particle size of 36 to 38 mμ (millimicra) that was in close agreement with sedimentation values obtained in the ultracentrifuge with similar preparation of the same and similar agents. Gradocol filtration determinations have indicated that some of the virus particles may be smaller than 20 mμ.

All strains exhibit complete resistance to diethyl ether, antibiotics, and some common antiseptics in the strengths in which they are usually employed. They survive prolonged exposure to a wide range of pH values and are inactivated only by temperatures from 51° to 60° C. or above for thirty minutes. Purified virus suspensions can be inactivated by chlorine but substantially more free chlorine is required to achieve comparable kills of Coxsackie virus than is required to kill *E. coli* cells.

It is interesting that type 1 virus differs from the others in group A in the clinical and pathological picture produced in mice. This strain represents one of the several group A types not yet associated with herpangina. Information is not available at present as to whether the other serological types in group A unassociated to date with human illness resemble type 1 or the strains causing herpangina.

Further details on the attributes of these viruses may be found in reviews by Melnick and Huebner.

LABORATORY DIAGNOSES OF COXSACKIE VIRUS INFECTION

Several procedures are available for the diagnosis of infection with Coxsackie viruses.

The method most often used is the isolation of virus in suckling mice from the fæces or oropharyngeal secretions, followed by immunological typing of the virus strains. Confirmation of infection is obtained when an antibody rise is demonstrated against the homotypic strain in neutralization tests performed on paired sera from the infected person. In many cases, however, complement-fixation tests show heterotypic responses to virus types other than the one isolated from the patient. These heterotypic responses are often equal to, or greater than, the response to the homotypic virus. On the other hand, such heterotypic responses are observed rarely if at all when sera are tested for neutralizing antibodies. For this reason the complement-fixation test is of limited value in the diagnosis of human infections. Some workers have advocated the complement-fixation test as a screening procedure for the general detection of recent Coxsackie virus infections but the usefulness of this test as a tool for epidemiological studies remains to be determined. The specificity of neutralizing antibodies, however, makes possible a serological diagnosis of infection provided that suitable paired specimens are obtained. This procedure requires multiple viral reagents and is therefore too cumbersome for general diagnostic use. Furthermore, unless tests are performed against all available agents, a negative result has little meaning.

Consequently, for the present, the diagnosis of Coxsackie virus infection remains the prerogative of research laboratories equipped to perform virus isolations, typing, and large numbers of serological tests.

HERPANGINA

Herpangina (vesicular pharyngitis, aphthous pharyngitis) is a specific febrile disease of childhood that occurs usually in epidemic form in the

summer and is characterized by the appearance of small to minute papular, vesicular and ulcerative lesions of the posterior part of the mouth and throat. It was first described by Zahorsky as a distinct clinical entity in 1920. Other physicians, apparently unaware of Zahorsky's original report, described outbreaks of similar illness in summer camps and nursery schools. As the result of controlled epidemiological studies involving the periodic surveillance of small residential communities for the presence of viruses and cases of illness, and by clinical and virological studies of herpangina alone, Huebner and his co-workers were able to establish six separate group A serological types as etiological agents of herpangina. Subsequent studies by Kravis *et al.* and Melnick *et al.* have offered confirmation that the group A Coxsackie viruses cause this disease.

Clinical aspects.—The illness usually begins acutely with a sudden elevation of temperature to 102° to 104° F. (38.9° to 40° C.). In the very young, vomiting and convulsions may accompany the rise in temperature. The patients may complain of headache, tenderness and pain in the abdomen, neck, or extremities. Anorexia and malaise are often present. The older children often complain of dysphagia and sore throat. During the first twenty-four to forty-eight hours, minute papular or vesicular lesions appear in the throat, followed shortly thereafter by 2 to 20 shallow ulcers with greyish bases surrounded by red areolæ. The fever usually reaches a peak during the first twenty-four hours and gradually returns to normal by the third day of illness. The pharyngeal lesions usually last one to five days. The lesions often persist for one to several days after defervescence but the patients are asymptomatic at this time even though the ulcerations may be large and coalescent. The lesions are seen most often on the anterior faucial pillars, less often on the soft palate, uvula, tonsils, and posterior pharyngeal wall. Rarely, lesions may be seen on the tongue or buccal mucosa but as a rule they are invariably absent from these sites. Signs of meningeal irritation are usually absent and the illness is not characterized by complications.

Except for the lesions in the throat, the other clinical manifestations of herpangina are quite non-specific and may resemble other mild diseases of childhood. So-called 'three-day fever' and 'summer sore throat' are examples of this kind. During preliminary community studies, Huebner and his associates encountered cases of illness in which the significance of throat lesions in several patients was not appreciated initially. These cases resembled the entity of 'three-day fever' described by Webb and Wolfe. Group A, type 2, virus was recovered from Huebner's cases and also from several of the cases described by Webb and Wolfe. Subsequent studies have shown that type 2 virus causes herpangina. Parrott *et al.*, studying cases of herpangina in an outpatient clinic, observed that siblings of patients with herpangina often had a similar illness manifested by a diffuse pharyngitis without ulcerative lesions; most of these patients harboured the same virus as their siblings who had typical herpangina.

Group A viruses produce herpangina as the most frequent and major manifestation of illness. It is possible that other gradations in the clinical spectrum occur, in between febrile illness with frank appearance of ulcers

	Herpangina	Acute herpetic gingivostomatitis
Etiology:	Group A Coxsackie viruses.	Herpes simplex virus.
Age:	1-7 years (occasional adult).	1-7 years, but adult as well.
Season:	Summer only (occurs in epidemics).	Year round (most in winter). Not in epidemics.
Clinical Features		
Nature of onset:	Sudden.	More gradual.
Fever:	100°-105° F. (37.8°-40.5° C.)	100°-103° F. (37.8°-39.4°C.).
Pain:	Mild in oropharynx.	Severe in oropharynx.
Pharyngitis:	Inflammation.	Not often involved.
Other signs and symptoms:	'Sore throat', vomiting.	Buccal membranes inflamed, gingivæ hæmorrhagic, fœtor-oris, local lymphadenopathy.
Oral or pharyngeal lesions		
Number:	2-14. May be numerous.	Few.
Type:	Vesicles, white-grey ulcer with areola.	Vesicles, white-yellow ulcers, areola not usually described.
Location:	Fauces, anterior pillars, soft palate.	Tongue, inner lips, buccal and sublingual mucosa rarely soft palate, pharynx and larynx.
Duration (days):	3-6.	10.

TABLE 3.—Differential diagnosis of herpangina and herpetic gingivostomatitis.

and inapparent infections. If this is so then the association of group A viruses with entities such as 'three-day fever,' 'summer sore throat,' and 'minor illness' may represent infection resulting in clinical variants of herpangina in which the pharyngeal lesions are less prominent. Careful, repeated examinations of the pharynx may resolve the diagnosis in many instances. Further observation is needed to clarify some of these problems.

Differential diagnosis.—The disease with which herpangina may be confused most easily is acute herpetic gingivostomatitis. Table 3 presents the distinguishing characteristics of these two illnesses. Herpangina may be distinguished readily from other illnesses such as thrush, the various 'aphthæ' of allergic, traumatic, or unknown origin, and measles, varicella, scarlet fever, and diphtheria. Heavy metal intoxications, deficiency diseases, and hæmatological disorders may also cause oropharyngeal lesions. As already mentioned, if in a case of herpangina pharyngeal lesions are missed, if typical lesions do not develop during observation, or if such cases occur sporadically and not epidemically, a specific clinical diagnosis is virtually impossible, since many mild illnesses of childhood exhibit fever and other less regularly observed symptoms of herpangina. The pharyngeal lesions

are quite specific, however, and when present they may be regarded as pathognomonic evidence of the disease.

Treatment.—Since herpangina is a mild, self-limited illness of short duration which does not respond to antibiotics, therapy is entirely symptomatic.

Epidemiology.—Herpangina is a disease of the summer and early fall months. Cases may be found in almost any community in which a search is made at this season. The group A Coxsackie viruses responsible for this illness have a wide geographical distribution and have been isolated in many parts of the United States, Canada, Europe, Scandinavia, Alaska, South Africa and the Middle East. As might be expected such coprophilic and resistant viruses have been isolated from sewage and flies.

Herpangina is a disease of the pædiatric age-group, although occasional cases may be seen in parents and inapparent infections may occur in adults. In some studies random selections of children in urban outpatient clinics have shown that as many as 10 per cent. will harbour herpangina strains during the summer months.

The usual incubation period for the disease is given as 3 to 4 days. A range of 1 to 9 days has been recorded.

There is strong evidence for the importance of familial or household exposure in the acquisition of infections with herpangina viruses. Observations on familial aggregation in cases of herpangina, on secondary infections, and on spread of herpangina among playmates indicate person-to-person transmission of the viruses. Serological studies of the same population at the same time have shown that nearly all susceptible persons within a household become infected once the virus is introduced, although all do not develop clinically apparent disease. Clinical studies in infected households have shown that only about 30 per cent. of infected persons manifest typical faucial lesions. A variable number of infected family contacts will present a similar picture of mild febrile illness without the typical throat lesions. In comparing the incidence of virus among various categories of persons in communities where infection was occurring, it was found that virus was recovered most often from patients with herpangina (85 per cent.), next in order of frequency from their neighbourhood (65 per cent.) and family (40 per cent.) contacts and least often from all other persons (3.5 per cent.) in the community.

Immunity to the infecting strains appears permanent, but the frequent presence of other strains provides ample opportunity for a repetition of the typical illness within the same or subsequent summer. Herpangina has been observed twice in succeeding summers in the same children and one child has been found to harbour two strains simultaneously. Each subsequent illness has been caused by a strain different from the one producing the initial illness observed. Most adults possess neutralizing antibodies against multiple serological types of herpangina viruses, the number of types increasing with age.

Differences in sex and race do not appear to influence the acquisition of infection.

EPIDEMIC PLEURODYNIA

Epidemic pleurodynia (epidemic myalgia, Bornholm disease, epidemic muscular rheumatism, acute benign dry pleurisy, epidemic pleuritic pain, Bamle disease, 'devil's grip') is an acute, specific, febrile, self-limited infectious disease, usually of children and young adults, characterized by: (a) abrupt onset of severe paroxysmal pain in the regions of the attachments of the diaphragm; (b) aggravation of the pain by movement and respiration; (c) periods of remission and exacerbation of the pain and fever; (d) frequent concomitant occurrence of severe headache, anorexia, and malaise. The disease usually occurs as sharply localized explosive epidemics, though endemic areas have been reported.

Daae and Homann first described the disease, in 1872, in Norway. Finsen had observed the disease initially, in 1852, in Iceland, but he did not publish his observations until 1874. In 1888, Dabney described the first outbreak of the illness in the United States. In 1933, Sylvest published his classical monograph describing his observations of patients on the island of Bornholm and reviewed the reports of European epidemics up to that time. Harder reviewed the literature on the American outbreaks up to 1935, and Scadding brought the subject up to date in 1946.

A viral etiology was postulated for many years but all attempts to isolate a virus failed until Curnen, Shaw, and Melnick, in 1949, reported the recovery of a strain of Coxsackie group B, type 1 (Conn. 5), from a single patient with pleurodynia. Subsequent reports from the United States and from Sweden have confirmed this agent as well as group B, type 3, virus as etiological agents in this disease. There is some suggestive evidence that types 2 and 4 may likewise produce pleurodynia.

Clinical aspects.—Table 4 lists some of the clinical features noted by various authors as a result of their observations of outbreaks of pleurodynia. The incidence of clinical features varies from one outbreak to another, and the manifestations of illness within a single epidemic may be quite protean.

The onset of the disease is usually sudden with few or no prodromal features. Characteristically there is acute onset of fever, headache, and anorexia accompanied by severe, paroxysmal, lancinating abdominal or chest pain which is aggravated by breathing or movement. The sensation of difficult breathing is usually quite striking. The patients often complain that it is difficult for them to breathe, or that they cannot get their breath. They attempt to obtain relief by splinting the affected portion of the chest or abdomen by means of a hand placed firmly over the painful area or by assuming a bent position with legs drawn up. This aspect of the disease has earned for it the colourful sobriquet of 'the devil's grip'. Onset of the illness with epigastric pain radiating to the lower anterior thoracic region occurs frequently. In many instances, between paroxysms or relapses, pain shifts from the abdomen to the chest or from one side of the thorax to the other. This illness has been called pleurodynia although in some outbreaks

pain is primarily abdominal in location; individual patients may have pain exclusively in the extremities or lumbar region of the back. Muscle tenderness accompanied by swellings of tender muscles with altered reflexes (especially of the abdomen) and paræsthesia has been described. Other less

Sign or symptom	Warin *et al.* 262 cases adults and children		McDonald *et al.* 70 cases children <15 years		Finn *et al.* 144 cases mainly adults <30 years		Howard *et al.* 22 cases adults		Total 468 cases	
	No.	%	No.	%	No.	%	No.	%	No. recorded	% of total recorded
Fever	Majority		70	100	109	95.7	18	81.9	206	95.7
Pain in abdomen and chest:										
Abdomen only	138	52.6	41	58.5	16	14.0	5	22.7	468	42.7
Chest only	52	19.8	7	10.0	55	48.4	7	31.8	468	25.8
Chest and abdomen	49	18.9	14	20.0	42	37.7	8	36.4	468	24.2
No pain abdomen or chest	23	8.7	8	11.5	1	0.9	2	9.1	468	7.3
Severe headache	90	34.3	42	60.0	50	43.8	12	54.5	468	41.5
Other signs and symptoms:										
Vomiting or nausea	40	15.2	22	31.4	27	23.6	8	36.4	468	20.7
Photophobia	31	11.8		—	1	0.9		—	376	8.5
Chills, chilly sensations or shivering	30	11.4		—	45	39.4		—	376	19.9
Sore throat	27	10.3	11	15.7	45	39.4	15	68.3	468	20.9
Anorexia		—‡		—	30	26.3		—	114	26.3
Head cold		—		—	18	15.7		—	114	15.7
Diarrhœa		—		—	8	7.0		—	114	7.0
Cough		—		—	38	33.2		—	114	33.2
Pain in limbs and muscle tenderness	18	6.8		—	16	14.0	16	72.9	398	12.6
Neck pains	13	4.9		—		—		—	262	4.9
Dizziness	11	4.2		—	6	5.3		—	376	4.5
Delirium	7	2.6		—		—		—	262	2.6
Paræsthesias	4	1.5		—	2	1.8		—	376	1.6
Complications:										
Orchitis	3	10% (adult male)		0	2	1.8	0	0	468	1.1
Friction rub	0	0	0	0	28	24.5	3	13.6	468	6.6
Pericarditis		—		—	1	0.9		—	114	0.9
Benign meningitis:										
Definite*	7	2.6	0	0	2	1.8	3	13.6	468	2.6
Probable†	9	3.4	0	0	2	1.8	2	9.1	468	2.8
Relapses	80	30.5	13	19.6	63	55.3	Frequent		446	35.0

*With pleocytosis. †Without pleocytosis. ‡Not recorded.

TABLE 4.—Incidence of clinical features in different epidemics of pleurodynia.

common features of the illness include nausea, vomiting, sore throat, and cough. The incidence of these features varies among different series of cases. Many patients complain of rather severe headache. Fever is usually present in the majority of patients. In children under two years of age the presenting feature may be convulsions along with the fever.

The average duration of the illness is four to six days in children and a little longer in adults. A range of one to thirty days has been reported. Recovery is often interrupted by recurrences of pain with fever; the fever usually reaches a peak when the pain seems most intense. Patients may have their initial symptoms for twelve to twenty-four hours, followed by an asymptomatic period of similar length; this is followed in turn by recurrence of pain and fever. After repeated recurrences, which may extend the illness up to three weeks or longer, some patients have residual soreness over the area of most intense pain, with a variable period of malaise thereafter.

The disease is usually self-limited but various complications have been described, the most common of which include orchitis (in adult males), pleurisy, and meningitis. The incidence of these complications is usually low but they have been described constantly enough so that one might perhaps consider them as less frequently encountered manifestations of the natural course of the disease rather than actual complications. In Finn's and Scadding's series benign dry pleurisy was quite prominent, and a group from Sweden has recently reported a high incidence of aseptic meningitis in children during an outbreak of pleurodynia. The significance of the latter complication will be discussed in due course. Other sequelæ described less often have been pneumonia, bronchitis, pericarditis, and otitis media.

Differential diagnosis.—When occurring as sporadic cases or at the beginning of epidemics, pleurodynia may be confused with appendicitis, biliary colic, acute cholecystitis, pancreatitis, perforated peptic ulcer, coronary insufficiency, pneumonia, pleurisy, pulmonary infarction, and occasionally the pre-eruptive phase of herpes zoster. These illnesses may be distinguished by the usual clinical and laboratory methods and they do not usually occur as epidemics during the summer or early autumn months. Cases of pleurodynia seen during the course of an epidemic should not offer much diagnostic difficulty.

Treatment.—Specific therapy is not available; management is entirely symptomatic.

Epidemiology.—Many epidemics of pleurodynia have been reported both in Europe and America. The basic epidemiological pattern of the early outbreaks was similar to that of more recent epidemics in which the group B Coxsackie viruses have been found as etiological agents. The seasonal prevalence of pleurodynia is summer and early autumn. The disease usually affects all age-groups but appears predominantly in children and young adults. Sharply localized outbreaks have been described in schools and colleges, military units, warships, small islands, convalescent homes, and orphanages. The disease has also been described in urban and rural areas. It has occurred endemically in Denmark, with over 10,000 cases reported to the Department of Health between 1930 and 1934. There was an increased incidence of the disease in the New York and New England

area of the United States in 1947 and 1948. In 1951, pleurodynia appeared locally in Texas and rather widely in Scandinavia, Holland and England. In contrast with herpangina, pleurodynia is not generally prevalent during successive summers in the same area.

Epidemiological evidence indicates that the disease is spread by contact among susceptible individuals. Virus is isolated usually from the fæces of ill persons and occasionally from the throat. Multiple cases occur either simultaneously or in succession in households, though many cases occur as single infections in households. On the basis of virological and serological studies of a rural outbreak, Huebner and his associates have found that many apparently susceptible household contacts may escape infection, but when group B virus is demonstrated in an area where pleurodynia is occurring it is nearly always associated with clinically apparent illness. The incubation period appears to be about 3 to 5 days, with a reported range of 1 to 18 days.

In a large urban outbreak, Warin and his collegues found that the weekly rate of incidence rose rapidly to a peak in four weeks and was followed by an equally rapid decline. In this and other similar outbreaks, cases were found throughout the urban district but the epidemics were characterized by local areas of very heavy infection. Socio-economic conditions, race and sex do not appear to influence the density of infection in most epidemics.

ASSOCIATION OF COXSACKIE VIRUSES WITH OTHER ILLNESS

Poliomyelitis.—The initial investigations of the nature of Coxsackie viruses were influenced by the fact that these agents were first isolated from two patients with poliomyelitis. The early reports indicated that the viruses were being isolated from cases of paralytic and non-paralytic poliomyelitis, 'aseptic meningitis,' and poliomyelitis-like syndromes. Various hypotheses were presented that Coxsackie viruses might influence the course of clinical poliomyelitis either favourably or unfavourably. A study by Cole and his associates, in which the reported incidence of isolation of Coxsackie viruses from poliomyelitis and non-poliomyelitis patients was compared statistically, indicated that these agents did not occur with any greater frequency among poliomyelitis patients than among normal populations or among persons with other illnesses in the summer and early autumn months. There is no good evidence at the present time that the simultaneous occurrence of Coxsackie virus infections with clinical poliomyelitis influences the course of the latter disease. Many Coxsackie virus infections, especially those caused by the group A strains, are clinically inapparent; the viruses occur abundantly in the pharyngeal secretions and stools of children during the summer months, they spread rapidly among exposed susceptible persons in households, community groups and hospital populations. These factors, plus the operation of chance, render the occurrence of Coxsackie viruses in a series of poliomyelitis patients of no more significance than their

expected incidence in a similar group of persons without poliomyelitis during the summer months.

In a continuing study of hospitalized patients with poliomyelitis from 1950 to 1952, Huebner and associates found that only 3.5 per cent. of 429 patients harboured Coxsackie viruses (mostly group A). Of the patients harbouring viruses, almost half appear to have become infected after they had been hospitalized for a short time. These results indicate that the isolation of Coxsackie viruses from hospitalized poliomyelitis patients may be explained partly on the basis of hospital spread of virus and in certain instances on the basis of carrier states or expected community incidence. In other studies of naturally occurring scattered epidemics of poliomyelitis, Huebner did not find an unexpectedly high incidence of infection with Coxsackie viruses.

Aseptic meningitis.—Benign aseptic lymphocytic meningitis is a clinical syndrome which has a varied viral and bacterial etiology. Among the agents often implicated in the production of this syndrome are lymphocytic choriomeningitis, mumps, herpes simplex, type 2 poliomyelitis (Lansing) and leptospirosis. In 1949, Curnen, Shaw, and Melnick described the isolation of group B, type 1 (Conn. 5), virus from children with aseptic meningitis. One patient from whom they isolated this virus had epidemic pleurodynia without signs of meningeal involvement. More recently, a Swedish group of investigators (Gabinus *et al.*) has described an outbreak of pleurodynia associated with group B, type 3, virus in which a high percentage of children had lymphocytic meningitis. Virus was isolated from the cerebrospinal fluid of one patient. This immediately raises the problem of the nature of the meningitis found in these circumstances. Several explanations may be postulated; the meningitis may be caused by: (1) the group B viruses isolated, (2) the other viral agents mentioned above, or (3) other as yet unknown agents. In the majority of patients with aseptic meningitis from whom group B Coxsackie viruses have been isolated, other viral agents (including poliomyelitis) have not been found.

Another problem raised by the finding of group B viruses in patients with aseptic meningitis is the relation of this syndrome to pleurodynia. Many epidemics of pleurodynia have been characterized by the occurrence of signs and symptoms of meningeal irritation in a variable percentage of patients. Sylvest, Pickles, and Huebner, however, found no such patients in their series. On the other hand, Howard, Finn, Warin, and others have described a small percentage of persons who showed signs of meningitis during the courses of their illnesses; lymphocytic pleocytosis of the cerebrospinal fluid was found in some of these. Most epidemics of pleurodynia have been reported before Coxsackie viruses were generally known; it is difficult therefore to assess the etiological nature of the meningitis occurring during these epidemics since the search for all viral agents was usually limited. Many of the patients with meningitis, however, also had evidence of pleurodynia and/or were related epidemiologically to other patients with

unquestionable pleurodynia. Typically, the aseptic meningitis associated with pleurodynia has occurred five to nine days after the onset of illness and usually with the second or third relapse. Except for the outbreak described in Sweden, meningeal involvement has been noted in less than 10 per cent. of patients in some large epidemics; positive cerebrospinal fluid findings, however, have been present in only a variable number of these cases. Pleurodynia is a disease of protean symptomatology; the pathology and pathogenesis of the illness are still unknown. It is conceivable therefore that involvement of the central nervous system and meninges may occur as part of the clinical spectrum in pleurodynia in much the same way that similar involvement occurs in mumps.

The Swedish group has advanced the hypothesis that group B viruses entering a highly susceptible population affect all age-groups with pleurodynia and myalgic symptoms as the predominating features, especially among the older children and adults; on the other hand, when children are primarily affected in a relatively immune population, aseptic meningitis may be a prominent feature. Even if this were so, the bulk of evidence at present seems to indicate that the major manifestation of illness produced by the group B viruses is the entity known as epidemic pleurodynia; at best, aseptic meningitis could be classified only as a minor manifestation of infection. The relationship of aseptic meningitis to pleurodynia and to the group B Coxsackie viruses is one that needs further clarification, and future well-controlled epidemiological, clinical, and etiological studies of naturally occurring outbreaks may provide some answers to this problem.

Other illnesses.—Sporadic isolations of Coxsackie viruses have been reported from a variety of unrelated illnesses. Such isolations probably represent inapparent, coincidental infections and have no etiological relationship to the disease which the patient had at the time.

SUMMARY

Some of the important properties of the Coxsackie viruses and the illnesses associated with them have been described. The Coxsackie viruses appear to be a family of viral agents of small particle size existing in multiple serological types and subdivided into at least two groups—A and B. They are prevalent in the summer, infect children mainly, are excreted *via* the stools, may be found in sewage and flies, spread rapidly by contact among susceptible individuals, and produce inapparent infections as well as overt illness. They appear to conform to the usual behaviour of most viral agents with respect to infectiousness, communicability and ability to confer long-lasting type specific immunity.

The two groups of Coxsackie viruses are distinguished by the differences in pathology of infection produced in their main laboratory host—the suckling mouse. With regard to human disease, group A viruses have been associated etiologically with herpangina and group B viruses with epidemic pleurodynia.

Present evidence indicates that clinical poliomyelitis is neither related to Coxsackie viruses etiologically nor is the clinical course of poliomyelitis modified by simultaneous infection with these agents.

The possible relationship of aseptic meningitis to epidemic pleurodynia has been presented and discussed.

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THE COMMON COLD AS A VIRUS PROBLEM

By A. T. RODEN, M.D., D.P.H., D.C.H.,
Medical Superintendent, Common Cold Research Unit, National Institute for Medical Research

THE term 'common cold' will be used throughout this article to denote an acute infection of which the predominant clinical manifestation is an increase in nasal exudate, or coryza.

THE CONCEPT OF THE COMMON COLD

How far it is possible, by clinical and epidemiological observations alone, to abstract such a concept from the generality of common respiratory diseases remains uncertain. Symptoms resembling those of the common cold are known to occur in functional disorders—hay fever, for example—which are not transmitted by personal contact; and the occurrence of these symptoms in an individual patient does not necessarily indicate an infective origin, even in the absence of all other recognized etiological factors. Moreover, the clinical manifestations of the common cold are not confined to coryza but include other symptoms such as sore throat, cough and feverishness, which vary in their relative intensity. Van Volkenburgh and Frost (1933), in a study of acute minor respiratory diseases, classified 1,388 cases by symptoms and found that nine-tenths exhibited coryza, two-thirds had cough, nearly one-half suffered from sore throat and about one-fourth exhibited fever. From their observations these authors concluded, among other matters, that the 'common cold' implies more than simple coryza and that the systemic reaction is more marked than is generally believed.

EARLY INVESTIGATIONS

Kruse (1914) and Foster (1917) showed that the common cold can be transmitted to man by means of bacteria-free filtrates of nasal secretions. From this it followed that the etiology of at least one group of common respiratory diseases could be considered in terms of infection with a filterable agent, or virus. During the subsequent forty years many workers have attempted, in various ways, to study the properties of such a virus, its clinical effects and its epidemiological behaviour. Two of the major obstacles to progress in this field of investigation have been: (1) the inability to demonstrate the presence of a common cold virus by any means other than its effects upon an animal host, and (2) the narrow range of species known to be susceptible to this infection. Dochez, Shibley and Mills (1930) described the experimental transmission of the common cold to chimpanzees, by means of a filterable agent, but attempts to transmit this infection to a wide variety of other

animals have proved unsuccessful (Andrewes, 1949). Methods of research have therefore been restricted mainly to human transmission experiments and epidemiological investigations unsupported by laboratory tests for the presence of virus.

DIFFICULTIES OF DIAGNOSIS

The results obtained by either of these methods have not always been easy to interpret, owing to uncertainties in diagnosis. In the absence of clinical or laboratory evidence of specific infections, such as measles or streptococcal pharyngitis, the distinction between the common cold and other forms of acute infective respiratory catarrh turns on the weight attached to particular symptoms or combinations of symptoms; and within the range of the common respiratory infections the points at which coryza ceases to be the dominant characteristic are subject to arbitrary definition. Nevertheless, some degree of differentiation has been achieved and clinically distinguishable types of infection have been described by several workers. Stuart-Harris *et al.* (1938), in a discussion of the differential diagnosis of epidemic influenza, refer to outbreaks of 'febrile catarrhs' in which sore throat and cough were the dominant respiratory symptoms and to outbreaks of 'simple coryza and pharyngitis' in which, accompanying the coryza and in some cases overshadowing it, there were sore throat and slight pyrexia. Judged by symptomatology alone, the cases of 'simple coryza and pharyngitis' or 'feverish cold', which these authors describe, would seem to occupy a position intermediate between the febrile catarrhs and the common cold.

In an attempt to segregate 'entities' from the group of unclassified respiratory illnesses, workers in the United States (Commission on Acute Respiratory Diseases, 1947) selected, for transmission experiments, four donors whose illnesses were classified, respectively, as 'acute respiratory disease', 'severe common cold', 'common cold' and 'bronchitis resembling atypical pneumonia'.

Nasal and pharyngeal washings were obtained from each of these donors and bacteria-free filtrates of the washings were administered to volunteers by intranasal instillation. Two types of illness were induced: one with an incubation period of 24 to 48 hours and coryza as the dominant respiratory symptom, another with an incubation period of 5 to 6 days and characterized by prominence of sore throat. In both types of illness the results of serological tests excluded the influenza viruses A and B as causative agents.

There is thus epidemiological evidence for the existence of several types of common respiratory infection and experimental evidence that at least two of them are associated with viruses other than those of influenza. More precise differentiation may be possible when laboratory methods for identifying the causative agents become available. In the meantime, human transmission studies, under controlled conditions, have remained the most important means of investigating the properties of these agents.

THE COMMON COLD RESEARCH UNIT

In 1946, a Common Cold Research Unit was established jointly by the Medical Research Council and the Ministry of Health. Workers at this

Unit confirmed (Andrewes, 1949) that common colds can be induced in groups of adult volunteers by the intranasal instillation of infective materials. These materials were obtained, in the first instance, from persons suffering from naturally acquired common colds. The method of collection was to wash out the nasal cavities with isotonic saline or broth saline solutions. Materials similarly obtained from volunteers suffering from experimentally induced common colds were tested in further groups of volunteers and were found to retain their pathogenicity after several passages: in one instance up to the eighth serial transfer from the starting material. At each passage-level, typical common colds were induced after a period of incubation, usually of 2 to 3 days. Respiratory symptoms or general constitutional disturbance falling outside the range of the common cold were of rare occurrence. These findings were consistent with the supposition of a transference from volunteer to volunteer of virus strains capable of producing a disease with a limited variation in its symptoms and signs. No evidence was obtained which suggested either an increase or a decrease in the virulence of these strains as a result of passage. When, however, volunteers infected with one of these 'pedigree' strains were used as donors in an experiment on the transmission of colds by natural routes (Andrewes, Lovelock and Sommerville, 1951), no clinical signs of the common cold developed in any of 12 volunteers exposed to risk of infection. This interesting result suggested that the strain used in this experiment might have changed its original character as regards infectivity: i.e., its ability to spread naturally from person to person.

Further studies on the natural transmission of the common cold (Lovelock, Porterfield, Roden, Sommerville and Andrewes, 1952) were made under controlled conditions, using people with 'wild' or natural colds of recent onset as donors of infection. Exposure of groups of adult volunteers for a period of two hours to risk of infection from these donors, by natural routes, was followed by the occurrence of common colds among the volunteers. It was found that the infection spread by normal social contact and also, in the absence of contact, by means of air-borne droplet nuclei, but the rate of clinical cross-infection under the conditions studied was low. Other methods by which common colds were successfully transmitted included administration of infective material by inhalation of mists and by means of moist nasal packs. Using approximately similar doses of the same infective material the highest proportion of 'takes' was obtained by the introduction of the material into the nose in the form of drops. This method has remained the standard technique for testing for the presence of common cold virus. Materials under test have been administered usually in quantities of 0.5 ml. into each nostril. This dosage is almost certainly many times greater than that acquired during natural transmission.

At the Common Cold Research Unit the proportion of colds induced by infective nasal washings, at dilutions not exceeding 1 :100, using the standard technique, has varied with different groups of volunteers. The average

attack rate has also varied, with no obvious seasonal differences, from year to year. It reached a maximum of 57 per cent. (52/91) in 1948 and a minimum of 27 per cent. (28/104) in 1952 (Andrewes, Chaproniere, Gompels, Pereira and Roden, 1953). These findings may be explicable in terms of differences between individuals as regards their resistance to infection by common cold virus strains. The testing of a given material has therefore necessitated the use of volunteers in numbers adequate to make a negative result unlikely if an infective dose of virus were present in the quantity of material administered. On the assumption that infective nasal washings will induce colds in 30 per cent. of the general volunteer population it can be calculated that a random sample of 12 volunteers will show a negative result approximately once in 72 trials. When using either materials or methods which give a lower clinical attack rate, larger numbers of volunteers are needed in order to attain the same level of confidence in a negative result. Moreover, the significance of positive findings needs to be checked by comparison with results in control groups of volunteers, to whom some inert material has been administered. For these reasons an organization for the attraction of sufficient numbers of suitable volunteers and their accommodation under conditions which minimize the risk of spread of natural infections has been essential to the conduct of the work of this Unit.

PROPERTIES OF THE COMMON COLD VIRUS

It is evident from the foregoing discussion that the uncertainties associated with human transmission studies may necessitate prolonged experimentation in order to verify quite simple assumptions and it is not surprising therefore that progress with such studies has been slow. Nevertheless, certain properties of common cold virus have been established as a result of them. By filtration of infective materials through graded collodion membranes (Elford, 1931) and subsequent testing of the filtrates for pathogenicity, the size of the virus has been estimated to be of the order of 30 to 70 mμ (Andrewes, 1953), which is considerably smaller than that of the influenza viruses. Infective materials have been preserved at −76° C. for periods of up to two years and have been found to retain their pathogenicity on subsequent testing. The virus can be inactivated by heating to 60° C. for one hour (Olitsky and McCartney, 1923) and there is evidence that it may also be inactivated by drying (Lovelock *et al.*, 1952). It would appear to be unaffected by either penicillin or streptomycin. Attempts to neutralize its clinical effects by means of nasal secretions from convalescent cases or from persons insusceptible to common cold infection have been unsuccessful.

The presence of common cold virus has been demonstrated, during the coryzal stage, not only in the nasal secretions but also in the saliva. There is evidence that it may be plentiful in the nasal secretions, during the incubation period, for at least 24 hours before the onset of symptoms and that it may also be present in the nasal secretions of persons in a normal state of health. The persistence of virus in the upper respiratory passages

of symptomless carriers may prove to be a factor in the spread of common colds. Transference of virus from a carrier to a susceptible person may account for some of the cases in which no history can be obtained of contact with a clinically recognized source of infection. Such sporadic cases may also be explained in terms of activation of virus already present in the nasal mucosa, although the etiological factors influencing this activation are imperfectly understood. There is no scientific evidence that chilling of the body surface will lower resistance to common cold infection, and it is uncertain whether local changes in the nasal mucosa can result in activation of the virus. Instances of the common cold apparently complicating coryza of vasomotor or allergic origin may be examples of such a process.

LABORATORY CULTIVATION OF THE VIRUS

Many attempts have been made to cultivate common cold virus in the laboratory. For some years, whole chick embryo techniques, which have been used for the cultivation of smallpox and influenza viruses, appeared to offer the most likely means of success. Several investigators (Kneeland, Mills and Dochez, 1936; Topping and Atlas, 1947; Pollard and Caplowitz, 1947; Ward and Proctor, 1950) claimed to have cultivated common cold virus in embryonated hens' eggs. In attempts to confirm these claims, workers at the Common Cold Research Unit employed four distinct techniques, each involving the inoculation of infective material into fertile eggs. Cultures from (1) the amniotic cavity, (2) the chorio-allantoic membrane, (3) the allantoic cavity, and (4) the yolk sac, were tested for pathogenicity in groups of volunteers. The results of these tests afforded no evidence of multiplication of a virus, or even of survival for as much as one passage (Andrewes, 1949).

Survival of common cold virus in cultures of embryonic human tissues was demonstrated in several experiments which were carried out at this Unit in 1949, with the collaboration of Dr. T. H. Flewett but, as no evidence for multiplication of the virus was obtained, no further tissue-culture experiments were undertaken at that stage. Of recent years the application of new techniques has resulted in a great expansion of interest in tissue-culture methods as a means for the cultivation of viruses. Enders, Weller and Robbins (1949) used tissue culture techniques for the cultivation of poliomyelitis viruses and, by similar techniques, a number of other agents has been studied in the laboratory. The multiplication of certain viruses in tissue-culture systems induces in the cells degenerative changes which can be examined in detail under the microscope.

This cytopathic effect affords a delicate laboratory test for the presence of such viruses, and examination of cultures for cytological changes has resulted in the discovery of other viruses whose existence was previously unknown. Rowe *et al.* (1953), in the United States, described the isolation of a cytopathic agent from human adenoids undergoing spontaneous degeneration in tissue culture and Pereira and Chaproniere (unpublished data) confirmed these findings and described a similar filterable agent isolated in

Great Britain. Hilleman and Werner (1954) cultivated a virus from throat washings from a patient with primary atypical pneumonia in an epidemic of acute respiratory disease during the winter of 1952-53, and stated that there was presumptive evidence of an immunological relationship between this virus and the adenoid degenerative agent. Laboratory tests for a number of known viral and rickettsial pathogens provided no evidence of relationship with the newly described agents.

It is uncertain whether these recently discovered viruses will be found to have any bearing on the subject of the common cold. Evidence has been adduced from human transmission studies (Andrewes *et al.*, 1953) that a common cold virus has been propagated through ten serial cultures of embryonic human lung, but in none of these cultures was a cytopathic effect observed.

CONCLUSION

Research on the virus origins of the common respiratory diseases has entered a most interesting phase. In laboratory investigations cytopathic agents have been discovered which, judged from their sites of isolation or from their association with acute respiratory disease, may well prove to be pathogenic to man: in human transmission studies filterable agents which induce common colds in man have failed to reveal their presence by means of tests in the laboratory. From the results so far obtained by each of these methods of research the indications are that further work with modern techniques of tissue culture offers the brightest prospect of elucidating the complex problems of the common respiratory infections.

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VIRUS DISEASE IN THE TROPICS

By G. W. A. DICK, M.D., B.Sc., M.R.C.P.Ed., M.P.H.
National Institute for Medical Research, London

Any of the virus diseases which are present in temperate zones may occur in tropical countries, but there are some (e.g. trachoma and lymphogranuloma venereum) which, although world-wide in distribution, are more prevalent in tropical countries. This is probably due to the poor economic and social conditions which are associated with low standards of hygiene in these areas. There are also some virus diseases which (so far as is known) are largely or entirely confined to tropical countries. It is these which will be discussed in this paper. Their localization to the tropics is chiefly due to the fact that the viruses which cause them are transmitted by biting insects which are not found, or cannot naturally breed throughout the year, outside the tropics. In addition, many of the tropical viruses are maintained in nature by cycles of infection which involve animals found only in tropical countries.

YELLOW FEVER

Human beings are infected with yellow fever virus by the bite of an infected mosquito. The clinical picture is very variable: from a completely asymptomatic infection to a fever of varying intensity which may be followed by severe toxæmia and death or recovery. The classical type of infection, which is rare, is characterized by jaundice, hæmorrhage and black vomit and is fairly readily diagnosed. The majority of infections, however, are asymptomatic or of a mild nature with the general symptoms associated with a fever lasting for two to three days. It is unlikely that such cases could be diagnosed clinically except during an epidemic. The virus circulates in the blood stream during the first few days of the infection and the clinical diagnosis may be confirmed by isolating the virus in mice which have been inoculated with acute-phase serum. Neutralizing antibodies appear a few days later and may be demonstrated by the protective effect which serum taken at this time has in mice inoculated with virus-serum mixtures. Such neutralizing antibodies (and immunity) are present for life and it is thus possible to make retrospective diagnoses. Extensive antibody surveys have been made to delineate zones of yellow fever activity and they have shown that in many parts of Africa yellow fever is present in places where it has never been clinically diagnosed and was believed to be absent. Diagnosis of fatal cases may be made by isolation of virus from the liver but is more commonly made by histological examination of pieces of liver removed by a viscerotome.

Infection with yellow fever is now confined to parts of Africa and South and Central America. Whilst there is only one immunological type of the virus, there are two epidemiological patterns of infection: a man-mosquito-man cycle and a cycle or cycles involving forest animals. In the former,

Aëdes ægypti mosquitoes are the unique vectors and, like other vectors of yellow fever, once infected they remain infective for life. The disease is maintained by mosquitoes and persistence of infection is dependent upon the presence of susceptible human beings and adequate numbers of *A. ægypti*. Since *A. ægypti* breeds in close proximity to human habitation in many parts of the world, this epidemiological type of yellow fever is known as *urban* yellow fever. As a result of control or eradication of *A. ægypti*, urban yellow fever is no longer present in the Americas. In Africa, *A.ægypti* is less domestic in its habits and much more difficult to control and it would appear that most of the recent rural epidemics of yellow fever in West Africa have been of the man-*A. ægypti*-man type. In spite of the eradication of *A. ægypti*, yellow fever still persists in the Americas where, as in Africa, there exists the *jungle* or *sylvan* type.

In *jungle* yellow fever there is a cyclic transmission of virus from forest mosquitoes to monkeys which, like human beings, circulate virus and provide a source of infection for other mosquitoes. It is possible that other forest animals, such as the opossums in South America and bush babies (*Galago* species) in Africa (Haddow, 1952), also play a part in the cycle of infection. Thus, the tropical rain forests in Africa and America contain a great reservoir of virus in infected mosquitoes which feed mainly on forest animals and the disease can thus persist in regions uninhabited by man who becomes accidentally infected from these forest cycles.

The spread of yellow fever to urban centres adjacent to the jungle foci and to more distant parts of the world depends largely upon the presence of *A. ægypti*. With air transport there is the serious threat of introducing travellers who are incubating the disease to areas where yellow fever is absent but where *A. ægypti* is present. This danger is of particular importance to India and the Far East where yellow fever has never occurred. To combat this eventuality there are international control measures which include quarantine of potentially infected travellers, the control and, where possible, eradication, of *A. ægypti* from airports, the spraying of aircraft with insecticides, and the vaccination of travellers to and from endemic areas*. Since yellow fever virus has not reached India in the past it seems unlikely that with the present sanitary precautions it will now do so. Several reasons for the failure of yellow fever to reach India have been suggested (see p. 574), but the most likely one is that there have never been any extensive epidemic foci of the disease in the adjacent East African ports from which the disease could readily spread. A similar argument could be

*It is not generally realized that even in the absence of *A.ægypti* yellow fever might occur in Britain. Thus, if a traveller who had escaped vaccination was infected in Africa or Central America, he could arrive in England during the incubation period. If he went to a woodland area he could be a source of infection to *Aëdes* (*F.*) *geniculatus* which in warm weather is plentiful in such places (P. G. Shute, personal communication) and is an efficient laboratory vector of the virus (Roubaud *et al.*, 1937). The disease could then be spread locally by *A. geniculatus* under suitable climatic conditions.

adduced for the absence of yellow fever in the Far East. Nevertheless, the potential danger of infection of clean areas is present in all parts of the world where *A. ægypti* bite human beings.

Complete protection against infection can be afforded by *vaccination*. Since control of the forest vectors and their animal hosts is not practicable, vaccination provides the only method of protection of those exposed to infection from the jungle cycles and of the populations of urban centres where anti-ægypti control is not feasible. There are two types of vaccines which are recognized: (a) 17D vaccine which consists of live attenuated virus which is grown in chick embryos, and (b) a vaccine prepared from the brains of mice inoculated with a neurotropic strain of yellow fever virus. The latter has been extensively employed by French workers but cannot be recommended because of the danger of encephalitis associated with its use.

Reactions after vaccination with 17D virus are uncommon and usually so mild as to go unnoticed, although a small proportion of those vaccinated may complain of headache or backache of a few hours' duration, coming on about a week after vaccination. Allergic reactions to 17D vaccine are extremely rare, but the possibility should be kept in mind in persons who have received previous chick embryo vaccines or have egg sensitivity. 17D vaccine may safely be given to infants and there are no contraindications to its employment. This vaccine is usually given by subcutaneous inoculation but it is equally efficient if administered by scarification. The latter method has considerable advantages for mass vaccinations. Attempts have been made to immunize with 17D vaccine combined with vaccinia by scarification. There is evidence to suggest that combination with vaccinia reduces the number who become immunized with 17D vaccine (Dick and Horgan, 1952). Whilst it is officially recognized that vaccination gives protection for six years following inoculation, there is now good evidence to show that neutralizing antibodies are present in the serum of vaccinated people for at least nine years and it is probable that after vaccination, as after natural infection, immunity is life long.

DENGUE

Dengue is caused by a virus which is antigenically related to yellow fever (and also to West Nile and Japanese B encephalitis viruses). It is transmitted by *A. ægypti* but in contrast to yellow fever there are at least two immunological types of dengue virus and more than one type may be present in the same area. This finding has an important bearing on the clinical picture. On first exposure to dengue virus the patient develops fever, sometimes of the saddle-back type of curve, and aches and pains in various parts of the body are characteristic. (The name dengue is from the Spanish *denguero* which means *dandy* and was presumably used because of the mincing or dandy-like gait of those suffering the aches and pains associated with the infection.) A maculopapular or scarlatiniform rash is commonly present from about the 3rd to 7th day of illness. Sabin and his collaborators (Sabin,

1952) have shown in human volunteer experiments that the immunity to one or other of the types of dengue is durable (up to at least 18 months), but if the volunteers were inoculated with one type of the virus and were then re-inoculated with a different (heterologous) type, it was found that the results depended upon the interval after the original infection. Thus, active immunity to heterologous types of virus was present up to two months, but thereafter the heterologous virus gave rise to a modified mild clinical disease with no rash. This important observation showed that in dengue areas where more than one immunological type of the virus was present pyrexias of unknown origin, not clinically recognizable as dengue, were indeed infections with that virus.

Dengue has a much wider distribution than yellow fever and extensive epidemics have occurred outside the tropics, e.g., in the countries of the eastern shores of the Mediterranean. A traveller who had returned by air to Britain from a warm climate might develop dengue in this country. The clinical diagnosis of such a case would be difficult and it is a laborious procedure (perhaps requiring human volunteers) to recover virus. A diagnosis may be made by serological tests of paired samples of serum, one taken early in the disease and the other taken during convalescence. An increase in antibodies in the second sample would confirm the diagnosis.

Since *A. ægypti* is the vector, the disease is essentially an *urban* one and it can persist in areas where relatively small numbers of *A. ægypti* breed continuously throughout the year. The reservoir of the virus in such places is *A. ægypti* and the virus is maintained if a sufficient number of susceptible children are born into the areas to keep the infection going. There is some evidence to suggest that there may also be a *jungle* type of dengue (e.g., in the Philippines). If such foci of virus activity do in fact exist they may, as in the case of yellow fever, represent the permanent reservoirs of the virus.

As has already been noted, yellow fever has never reached India or the Far East, yet *A. ægypti* and dengue are prevalent in these areas. The most probable reason for this has already been mentioned. Another possibility has been suggested by experiments of Sabin and Theiler (Sabin, 1952) which showed that if dengue-infected *A. ægypti* were also infected with yellow fever virus there is interference with the multiplication of the yellow fever virus and the mosquitoes fail to transmit the latter by bite. This suggests that if yellow fever were introduced into areas where it has never been but where dengue is endemic (e.g. India, the Far East, Australasia) the *A. ægypti* in these areas might be refractory to infection with yellow fever virus because they were infected with dengue and thus yellow fever would not become established.

Control of the disease in urban centres is dependent upon the control, and, where feasible, the eradication, of *A. ægypti*. As a result of studies made during the 1939-45 War, Sabin and Schlesinger (Sabin, 1952) developed a vaccine which was effective in immunizing human volunteers. This vaccine has not yet been used in a field trial as the war came to an end

before its effect could be tested in troops destined to enter an endemic area. It may, however, be expected to prove effective should its use ever be required.

WEST NILE VIRUS INFECTION

West Nile virus was first discovered in Uganda and antibody studies have shown that it has a wide distribution in Central Africa. Infection with this virus is also prevalent in Egypt and Israel where strains of the virus have been isolated during epidemics of the disease. The main symptoms are fever of two to three days' duration, and a macular or papular rash is often present in young children infected with this virus (Bernkopf, *et al.*, 1953). The absence of a rash in the majority of older children and adults makes one wonder whether there may not be multiple immunological types of West Nile virus and whether the clinical picture in many adults may not indicate a response to re-infection with a heterologous type (*cf.* dengue). A pyrexia of unknown origin in a traveller who has returned from Africa or the Middle East might be due to West Nile virus. The virus is readily recovered from blood taken during the acute phase of the infection (such samples should be kept on ice before and during transmission to a diagnostic laboratory). Immunity after infection is probably durable.

The virus has been recovered in nature from at least two species of Culex mosquitoes and all the epidemiological evidence suggests that it is a mosquito-borne disease. Very little is known as to how the virus is maintained in nature, but it would appear that there is a cycle or cycles of infection involving birds from which the virus has been isolated (Work *et al.*, 1953). Whether birds are the central element and natural reservoir of the virus is not known.

JAPANESE B ENCEPHALITIS

Japanese B encephalitis occurs not only in Japan but also in South-east Asia —in the Philippines, the Malay Peninsula, Sumatra, Borneo (Pond *et al.*, 1954). It belongs to the group of summer encephalitides in which are included the equine encephalitides and St. Louis encephalitis of North America. The virus circulates in the blood stream during the first few days of infection and it seems probable that transmission to man and from man-to-man is by mosquitoes, although this has not yet been definitely proved. The virus may be experimentally transmitted by Culex mosquitoes which have also been found naturally infected with it.

Whilst many infections with this virus are subclinical and can only be recognized by antibody studies, it may produce meningo-encephalitis and death. In a proportion of cases recovery is associated with neurological and psychotic sequelæ. There is nothing highly specific about the encephalitis which would make it possible to diagnose the illness as being due to Japanese B virus, unless the virus were identified in the laboratory.

The reservoir of the virus is unknown. Birds and many mammals have been suspected. It appears that the virus can be active among domestic

animals at a time when it is not producing infection of human beings. In Malaya, infection of race horses is prevalent but they do not represent the reservoir of infection.

Since mosquitoes are suspected, control measures and protection should be taken against them in endemic and epidemic areas. Quarantine of travellers ill with the disease should prevent possible spread to other areas. A chick-embryo vaccine has been used to protect laboratory workers engaged in studies of this virus. There is no information as to the efficacy of vaccination in the field.

RIFT VALLEY FEVER

The virus of Rift Valley fever was first isolated in the Rift Valley of Kenya. It is primarily a disease of cattle and sheep, among which it has caused serious enzöotics in Kenya and in South Africa. There is a certain amount of evidence which suggests that it is transmitted among animals by mosquitoes. Infection of human beings is an accidental event in the natural history of the disease. Only those in intimate contact with infected animals, carcases, and possibly milk, contract the infection. The symptoms are those commonly associated with pyrexia of a few days' duration. Complete recovery is usual but retinal complications with loss of vision have been described as an important and not uncommon complication in South Africa (Freed, 1951).

It is not known how the virus is maintained in nature. It is probable that, at least in Central Africa, there is a sylvan cycle which involves neither domestic animals nor man.

OTHER TROPICAL VIRUS DISEASES

Phlebotomus fever (*syn.*, sandfly fever), which as its name implies is transmitted by the genus *Phlebotomus*, is prevalent in the dry areas of the tropics where that insect is found. The symptoms are those of mild influenza and somewhat similar to those in persons who have been reinfected with heterologous strains of dengue virus. It is doubtful if an accurate clinical diagnosis can be made except on epidemiological grounds. Control of the disease depends upon the control of the vector by insecticides. Nothing is known of the way in which the virus is maintained in nature apart from man-*phlebotomus*-man cycles.

Bwamba fever is a specific viral infection of man in Central Africa and gives rise to symptoms similar to those of phlebotomus fever. There is some circumstantial evidence which suggests that this virus may have a jungle cycle involving monkeys. Its vector is not known.

Viruses of the *encephalomyocarditis-Mengo encephalomyelitis-Columbia-SK* group have been incriminated as the causative agents of 3-day fevers in Manila, and encephalitis due to a member of this group has been described from Uganda. Claims have also been made by some American and European workers that this group of viruses may be responsible for poliomyelitis-like symptoms. It must be stressed that there is no evidence whatsoever to suggest that this group is in any way related to poliomyelitis. So far as is

known, the natural reservoir of this group of viruses is in rats (genus *Rattus*) which apparently suffer no ill-effects from harbouring the virus (Dick, 1953). It is not known if this group is present in Britain. The viruses can readily be recovered from human infections by inoculating mice with acute-phase serum; immunity is durable, lasting for at least seven years after infection.

Mention should also be made of *Ilhéus virus* of Brazil and *Venezuelan equine encephalomyelitis virus*. The latter, although primarily a disease of equine animals, has recently been shown to be capable of causing human epidemics in Colombia, with symptoms which in the tropics might be diagnosed as 'atypical malaria' or 'grippe' (Sanmartin-Barberi *et al.*, 1954). This brings us, in conclusion, to a list of tropical viruses which have been isolated from mosquitoes by Smithburn and by Dick and their colleagues in Uganda. Antibodies to these viruses have been found in the sera of residents of not only many parts of Africa but also of India, Malaya and North Borneo (Smithburn, 1954). These viruses have been given the names of the places in Uganda where the isolations were made and are as follows: *Semliki forest, Bunyamwera, Ntaya, Uganda S and Zika viruses* (for references see Dick, 1953). *Zika virus* has also been isolated from human beings and monkeys and there is some evidence which suggests that it may produce jaundice in human beings (Macnamara, 1954). Nothing is known of the diseases which the other viruses cause in man.

TREATMENT AND PREVENTION

In this brief review of the present status of virus diseases in the tropics no mention has been made of treatment. With the exception of trachoma and lymphogranuloma venereum there is as yet no specific treatment for any of them. Application of known control measures which have been discussed depends upon the money available to carry them out, and on decisions as to which diseases are having the greatest economic effect on the country concerned or are of most importance from their possible spread to other countries. In general their prevention depends upon a complete understanding of their epidemiology. Meanwhile, many of these virus infections may have to be accepted as possible hazards of life in a tropical country.

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VIRUS DISEASE IN GENERAL PRACTICE

By G. I. WATSON, M.D.
Peaslake, Surrey

'In many ways one can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of infectious disease as a significant factor in social life'. (Burnet, 1953.)

'With bacterial and protozoal diseases coming under better and better control, the viruses loom relatively larger in their importance for man's health and happiness'. (Andrewes, 1953.)

THE importance of virus disease in general practice can be gauged from an analysis of the figures in my own practice—a country practice in the south of England.

SOME STATISTICS

During the last five years between 16 and 29 per cent. of patients visited at home were suffering from a disease caused, or possibly caused, by a virus. This does not include those who were well enough to come up to the surgery with warts, coryza, herpes simplex, and the like, or for vaccination. The incidence of individual diseases would no doubt vary in other practices and in different parts of the world, even more than they did from year to year in this district. In table 1 the yearly totals of these cases are given to illustrate these fluctuations.

	1949	1950	1951	1952	1953	Totals
Coryza	40	87	50	27	31	235
Influenza	27	43	53	33	65	221
Measles	7	29	127	5	35	203
Mumps	51	—	16	14	8	89
Chickenpox	8	4	7	32	11	62
Pyrexia of unknown origin	9	15	10	4	15	53
Rubella	—	15	15	12	6	48
Herpes zoster	12	5	2	3	—	22
Epidemic winter vomiting	—	—	—	5	14	19
Infective hepatitis	4	2	2	3	2	13
Bornholm disease	—	—	1	4	2	7
Undiagnosed fever and rash	—	—	3	2	1	6
Acute vertigo	—	—	—	2	1	3
Glandular fever	—	1	—	—	1	2
Primary atypical pneumonia	—	1	—	—	1	2
Encephalitis	1	1	—	—	—	2
Poliomyelitis, paralytic	—	—	—	1	—	1
Poliomyelitis, non-paralytic	—	—	1	—	—	1
Total virus diseases	159	203	287	147	193	989
Total new visits	942	978	975	893	810	4598
Percentage due to virus diseases	17	21	29	16	24	21

TABLE 1.—Annual totals of virus diseases seen in a country practice (patients ill in bed).

At the present day, when the bizarre and the fantastic are so often in the news, it is perhaps reassuring to find that the common cold is still in fact

the commonest virus disease in general practice. And the big five—influenza, measles, mumps, chickenpox and rubella—are all well placed. But the tail of the dog is growing steadily and a new name seems to appear almost every year, while a few old friends, such as 'gastric flu' and 'catarrhal jaundice', have been dignified by longer titles.

It happens that in this district poliomyelitis has not been prevalent but fear of it is none the less widespread, and perhaps for this reason one is nowadays asked to see a larger proportion than before of the short-lived pyrexias of unknown origin. This has been valuable in calling attention to the prevalence, during the summer and autumn months in most years, of cases which broadly correspond to those described by Curnen and his colleagues (1949) in Connecticut and by Huebner and his colleagues (1950) in Maryland, with which Coxsackie virus was associated. The few days which must pass in each case, before poliomyelitis can be excluded, may be anxious alike for the doctor and the child's parents, while adequate laboratory facilities for differentiating virus diseases are still a thing of the future.

The diseases caused by viruses, as opposed to those of bacterial origin, have been thrown into prominence by the therapeutic filter of the sulphonamides and the antibiotics. These now deal so promptly with so much of the acute illness seen in general practice that not only the patient, but even the practitioner, is tempted to impatience by the failure of these agents to shorten or alter the course of most virus diseases; and indeed the first step in diagnosis of such a condition as virus pneumonia may only be taken after the patient has failed to respond to adequate doses of penicillin.

All the qualities of the old-time G.P. are still called for in dealing with this group of infectious diseases: diagnosis, nursing instructions, treatment, epidemiology and research, all still have their proper place here.

DIAGNOSIS

The diagnosis of the different virus diseases can sometimes be extremely easy; at other times the disgnosis may remain in doubt for many days and indeed may not be made at all. Classical measles, mumps and chickenpox during epidemics usually present no difficulty, but in a child who is said or known to have had measles or rubella in the past, the diagnosis of any subsequent febrile rash may call for all the skill (and tact) that a doctor possesses. It is possibly wise to discount a mother's story of her child having had measles or German measles under the age of 2 years, if she is able to say for certain that there was no epidemic in the district at the time; whatever the correct diagnosis may be in these solitary cases of 'erythema infantum', no doctor will be in practice for many years without being puzzled by such a case.

In the diagnosis of poliomyelitis, glandular fever, Bornholm disease, and particularly infective hepatitis, the most important help is to have the condition in mind. In infective hepatitis, French (1954) found that vomiting

was a presenting or early symptom in every single case out of 28 children, whereas in adults this was not necessarily true. Laboratory assistance with the diagnosis may be obtained in the case of infective hepatitis, glandular fever, psittacosis, virus pneumonia, Rickettsial diseases and, recently, influenza, but in the case of poliomyelitis and the Coxsackie viruses the routine examination of specimens is not yet feasible, although such can be undertaken in special cases or for research purposes. In some cases of doubt about the nature of a feverish illness, the finding of a normal or lowered leucocyte count, and particularly the absence of granulocytosis, may assist in ruling out the presence of pyogenic infection; but the absence of leucopenia does not rule out a virus infection.

NURSING INSTRUCTIONS

Not many years ago the nursing of a case of typhoid fever reputedly might embrace every aspect of a nurse's training and skill. So far as home nursing is concerned the same is probably still true of both influenza and severe measles. In these two diseases, and in serious examples of some of the others, a general practitioner has the opportunity to make a considerable contribution to the comfort, and indeed safety, of his patient, if advice is given about a number of points which almost invariably arise. In influenza, as soon as the diagnosis is established, it is wise to point out that fever is likely to continue for about five days, irrespective of any antibacterial drugs which may be given. Likewise in the case of measles it reassures a mother to be told, on the day when the rash appears, that it is a self-limiting illness, and that high fever is unlikely to continue beyond the second night; at the same time she should be warned that, on the evening of the day when the rash appears, the temperature, especially in summer, may easily reach 105°F. (40.5°C.). She should be encouraged not to overload the child with bedclothes, to ventilate the room as well as circumstances allow and, in a child who seems unduly hot, to watch for the early twitching which may precede a convulsion. If such an event is thought likely, the doctor should instruct her about tepid sponging, and if she is able to read a thermometer I usually advise that sponging should be begun when the temperature in a young child reaches 103°F. (39.5°C.), and should be continued for five or ten minutes every half hour so long as the temperature continues to rise.

In cases of influenza, especially among the elderly, thought must be given to see that the patient's needs for toilet and personal hygiene can be provided. It may be possible for the District Nurse to help in such cases if the patient's family are not able to deal with the problem on their own, but in every epidemic of any size, both in rural and in urban practices, there will be occasions when such a patient needs admission to hospital as much for social as for medical reasons. In the case of poliomyelitis and of those pyrexias of unknown origin which simulate its early stages the emphasis should be on personal hygiene as regards both the patient and his immediate

attendants. The ideal would be that separate toilet facilities for the patient alone should be available in the sickroom.

In the case of mumps, particularly in boys about the age of puberty, it will be difficult to enforce a sufficient period of rest in bed unless the reasons for this, if not already known, are explained to one of the parents. In this disease, in measles while the rash is fading, and in infective hepatitis while waiting for the jaundice to diminish, the modern child has a real advantage over his forebears in the variety of amusements which can now be provided in the sickroom.

Probably every doctor's wife has been asked for her secret advice in helping to deal with some problem of a patient's diet. Another excellent source of information, with a dull-sounding title, is the 'Manual of Nutrition', published inexpensively by H.M. Stationery Office. In all feverish illness, and particularly in infective hepatitis, the choice of suitable food and drink for the patient is a subject that will repay a doctor's attention. The end of food rationing has made it easier but no less expensive to provide the quantities of lean meat needed in the latter disease. When extra glucose is needed, for example to counter the ketosis that may accompany high fever or follow repeated vomiting, it is more effective to give this hourly in the form of half-teaspoonsful of the dry powder washed down with a favourite drink, rather than to rely on any of the various brands of sweetened drink that are on the market; apart from being cheaper it saves the patient having to drink more than he may be able to retain, in order to consume the necessary amount of glucose.

TREATMENT

'It is our present helplessness to cure most virus diseases of animals which makes these diseases increasingly important' (Andrewes, 1953). Nursing and treatment should not logically be separated, particularly in virus diseases when curative remedies are as yet scarcely available. Nevertheless, the drug treatment of many of these conditions is important, if only because of the bacterial complications by which some of them are followed.

CORYZA AND INFLUENZA

Coryza.—Whilst it may be true that there is as yet no cure for the common cold, this does not mean that none is attempted by almost every sufferer. Perhaps the three most common ingredients are a hot bath, a hot drink (preferably with 'something' in it), and aspirin. It would be of considerable interest to a large public if the separate and conjoined actions of these three remedies could be studied, perhaps at the Common Cold Unit, as were the antihistamines a few years ago.

Influenza.—The three sovereign remedies mentioned above have usually already been tried, and found wanting, before a doctor is called to see a case of influenza. From the general practitioner's point of view the aim of drug

treatment is to allow his patient to endure his five days or so of fever with the minimum of discomfort and the maximum freedom from complications. Codeine is the drug of choice to allay the irritating cough but the most useful antibacterial prophylactic in both influenza and measles has yet to be determined. There are theoretical objections to using the sulphonamides in any disease associated with leucopenia, but this is a matter that is still being investigated.

For the relief of pain an aspirin compound in occasional doses is excellent and can do no harm, but the wisdom of giving frequently repeated doses of aspirin or salicylate mixtures as antipyretics is one to which, perhaps, some further thought should be given. Considerable similarities have been found between the action of salicylates and cortisone in rheumatic diseases (Joint Committee, 1954) and enough is known about the action of cortisone in depressing the inflammatory reaction and a host's resistance to parasitic infection to make it certain that no-one would advise using cortisone as a routine in influenza. Have aspirin and the salicylates a similar action on a patient's resistance to bacterial infection? Should a warning be issued against the liberal use of these drugs in febrile patients who have, for example, a past history of infection by tubercle bacilli? (The only adult patient who developed pulmonary tuberculosis in this practice during 1953 did so following an attack of epidemic influenza for which he had been treating himself with codeine tablets four-hourly for several days.)

MEASLES AND MUMPS

Measles.—Prophylactic treatment of children against measles is possible with gamma globulin which, because of scarcity, was until recently restricted in its use in this country to children under two. This restriction seems to have been based on the assumption that the observed severity of measles in young children in days gone by was due as much to effects of the virus infection as to the bacterial complications which ensued. The correctness of this assumption, however, has been questioned by a number of practitioners since antibacterial drugs became freely available. For several years sulphonamides have been increasingly used in the prevention of the bacterial complications of measles but their action may be only curative rather than strictly prophylactic, though this may not be the case with penicillin. These problems are at present under investigation by a group of about 130 doctors in the College of General Practitioners. In the drug treatment of the virus illness of measles, there is no doubt that aspirin in some form is of value during the hyperpyrexia which often occurs while the rash is appearing. A really satisfactory drug for the treatment of the cough has yet to be found; at present codeine is probably the best available.

Mumps.—Drugs play a very small part in the treatment of uncomplicated mumps. For the treatment of pancreatitis some form of morphine or pethidine is usually required. Chloramphenicol and 'aureomycin' (chlortetracycline)

are expensive drugs, but the virus of mumps appears to be sensitive to these antibiotics and their use may occasionally be justified.

CHICKENPOX AND RUBELLA

Chickenpox.—Gamma globulin prepared against chickenpox is not available in this country and its use in any case would seldom be called for; but on the assumption that most people who have had measles have also had chickenpox, I once used large doses of measles gamma globulin with apparently good effects in a non-immune mother six weeks before term, the rest of whose family had contracted chickenpox. She produced altogether only four vesicles on one arm, and I am waiting now to see whether or not her baby has acquired an immunity. There seems no doubt in the minds of patients who have used them that the antihistamine drugs give considerable relief in the irritation which accompanies the eruption in this disease. They seem also to prevent the vesicles enlarging as much as in untreated cases. Penicillin orally or by injection may be necessary in a few cases, especially girls, to counter the bacterial infection in vesicles and so diminish the scarring.

Rubella.—In the light of our new knowledge about the effects of rubella on the fœtus in early pregnancy, it has become important to try to ensure that every girl has her attack of rubella in childhood or adolesence rather than observing any quarantine, apart from that which is needed to protect mothers in early pregnancy. Whether some form of anti-rubella vaccination, or even 'German measles tea parties', would ever help to overcome this danger only future research can tell; the use of rubella gamma globulin for the protection of mothers who have been exposed to this disease in early pregnancy is already being investigated. Drugs play scarcely any part in the treatment of the established disease.

'P.U.O.' AND POLIOMYELITIS

It may not seem logical to group such an important condition with other ill-defined fevers, but in fact every case of poliomyelitis which does not present with paralysis starts as a case of pyrexia of unknown origin. The essential treatment for all these cases is rest in bed from the time the fever is detected, and the lesson cannot be preached too widely by general practitioners that every fever during the summer and autumn months should be considered as due to poliomyelitis until events prove it otherwise. It is far better to be still uncertain of the diagnosis after a child has fully recovered, than to know that the diagnosis is paralytic poliomyelitis. Likewise it is better to withhold all drugs, even aspirin unless headache is severe, and so get a truer picture of the rise and fall of the temperature. (I encourage all parents with children at home to learn to read a thermometer and to write down their records for me.) Once paralysis appears in a case of poliomyelitis, consultant advice will be taken about where the patient should be nursed, according to whatever facilities are available at home and in local hospitals. If a long ambulance journey has to be made by a patient with laryngeal paralysis, the general

practitioner may save the patient's life by ensuring that he travels in the prone position, not lying on his back.

HERPES ZOSTER

The two aims of treatment in this condition are to prevent the eruption being broken and to minimize pain. For the former an occlusive dressing such as collodion, painted repeatedly over the eruption, is usually satisfactory. Although pain is always expected by the patient it is surprisingly often quite mild; when at all severe it is likely to be persistent, at least for some weeks, and for this reason codeine, which is not habit forming, is to be preferred to pethidine or morphine. The patient should take a sufficient dose of codeine tablets at one time to give reasonable relief from pain, rather than take smaller doses and have to repeat them more often. In a severe case as the weeks go by, he can be encouraged to look on his diminishing score of tablets every twenty-four hours as a measure of his improvement. For the relief of pain, injections of crude liver or vitamin B_{12} have been advocated but are not always effective. The use of broad-spectrum antibiotics has been encouraged on the grounds that they were effective against the virus but this again has not been borne out in practice. Their use, however, in the form of eye-drops, is helpful in reducing bacterial infection in zoster ophthalmicus.

SOME OTHER VIRUS DISEASES

Epidemic winter vomiting.—From personal observations I believe that during the acute phase of vomiting which occurs in this condition, so often starting in the night, nothing at all by way of food or medicine should be given by mouth as it tends to increase the vomiting. Afterwards dehydration or ketosis often require treatment.

Infective hepatitis.—Drugs, as opposed to diet and rest in bed, play scarcely any part in the treatment of infective hepatitis.

Bornholm disease.—For the relief of pain in this disease, known to be of short duration, the use of pethidine, if necessary, is justified. The wisdom of giving antipyretics in these cases is subject to the same remarks as were made under influenza.

Acute vertigo.—Whether this condition is in fact an infectious disease, and if so whether it is due to a virus, is not yet known. All that can be said is that it seems at times to appear in epidemic form and there has recently been a prevalence of this condition in N.E. England (Research Newsletter, 1954). During the acute stage of severe vertigo there is no drug which will allow the patient to move about without aggravating his symptoms, but 'sedation with phenobarbitone with the administration of nicotinic acid had a valuable influence' (Yuille, 1954).

Glandular fever.—There is no drug which will shorten an attack of glandular fever and, because the febrile stage may be prolonged, the regular use of antipyretics is probably unwise. The use of sulphonamides is

contraindicated because of their possible effect on blood-forming tissues, but penicillin may be required in the treatment of the sore throat.

'*Virus pneumonia*'.—In general practice one is tempted to make this diagnosis when a case with pneumonic signs does not respond in the expected manner to penicillin treatment. On further investigation, if the cause is a virus the correct diagnosis may prove to be influenza, 'Q' fever or primary atypical pneumonia; strictly speaking, however, the term is reserved for those cases in which cold agglutinins are present in the serum. Such cases, and also those caused by the psittacosis virus and *Rickettsia burnetii*, are susceptible to treatment by chloramphenicol and chlortetracycline ('aureomycin'). Some cases of psittacosis have responded to sulphonamides but the majority are resistant; penicillin, however, has given good results and for this reason such cases may not be suspected or correctly diagnosed unless one's attention is drawn to the patient's contact with birds.

EPIDEMIOLOGY AND RESEARCH

'It is therefore no idle boast for us to say that we stand on a strategic pinnacle for the investigation of infectious disease' (Pickles, 1939). The view from that pinnacle is constantly changing and one never knows what will next appear in view or what discoveries await us: '. . . discoveries made, not by experts, but by medical practitioners working patiently on the lines of Dr. Pickles' (Greenwood, 1939). So many features still remain unknown, even about the commonest of the virus diseases. For example:—

(a) The duration of infectiousness before and after the onset of symptoms: only now are the limits of infectiousness beginning to be accurately measured. In a personal communication, Dr. R. E. Hope Simpson of the Public Health Laboratory Service Epidemiological Research Unit gives the following figures for the 'safe interval' during which susceptible contacts may mingle freely with other susceptibles, with a 90 per cent. security:— Measles—4 days after the worst day of rash in the patient; chickenpox—7½ days after the first appearance of rash in the patient; mumps—10 days after the first appearance of swelling of any gland in the patient.

If we could measure for each disease the duration of infectiousness within certain limits of safety, this might lead to a policy of isolation of susceptible contacts only during possible infectiousness, not throughout the incubation period.

(b) Do secondary cases in a house have more severe measles and chickenpox than the primary case in the same family? Ideas like this may occur to one, yet in some practices it may be several years before a general practitioner, single-handed, can collect enough examples to answer the question he has posed.

(c) The epidemiology of influenza and poliomyelitis between epidemics is still incomplete. The Public Health Laboratory Service at Colindale has for the past year or two enlisted the help of 'spotters' throughout the country,

who would send in certain specified samples from suspected cases of influenza throughout the year. This sort of work depends for its success partly upon the number of 'spotters', more perhaps upon their keenness and readiness at a moment's notice to go a little out of the way of their ordinary routine.

(d) New ways of studying the epidemiology of diseases such as glandular fever, acute vertigo, and even perhaps Bell's palsy, are needed. Of such conditions any one doctor may not see many cases in a year but in cooperation with others he could add his quota of observed facts.

(e) Apart from such epidemiological research, there are many opportunities for studying more closely the medication of acute virus diseases, and especially of their bacterial complications, both prophylactic and curative.

(f) Finally, but none the less important, there is need for a more accurate definition of the various febrile syndromes, with and without rashes, which make their sudden appearance from time to time in different parts of the country, so that others can recognize them when they recur elsewhere; and these records should be published.

Evidence is increasing that many general practitioners have kept such records, sometimes for many years, but in any one practice the number of good examples mounts all too slowly. To overcome this difficulty an attempt is now being made by the epidemic observation unit of the College of General Practitioners to collect and publish such records, either about particular problems or about 'queer cases' and other occurrences which are out of line with general experience. It may therefore be a fitting conclusion to echo words which were once written by the President of that College (Pickles, 1939) about this very problem: 'I have known several country practitioners with useful knowledge to impart, gathered from their own observations, but who considered it too trivial even to write down, much less publish. Nothing, I believe, is further from the truth, and by withholding these observations from the public, these men are damming up sources of information that are among the only accurate ones from which such information can be drawn. It is probable also that these opportunities will not remain available indefinitely'.

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HEALTH AND NORMALITY IN CHILDHOOD

By CEDRIC C. HARVEY, M.D., M.R.C.P., F.R.C.S.Ed.
Pædiatrician, West Riding County Council and Rotherham Hospitals

'Guiding and guarding with devoted mind
The tedious generations of mankind'.

Zestful and insatiably curious, proud of new skills, forthcoming yet with private reserves, poised and withal spontaneous, taking denial gracefully, fresh off the mark in the morning, climbing with alacrity into bed at night, and falling promptly into relaxed sleep: such children we would wish for all our patients. But Kipling's Four Archangels will be hard pressed to help them achieve the ideal, not once but repeatedly in each family.

Practice with children is more interesting than with the adult, for it covers additional territory. Whereas in adult medicine disease consists in deviation away and down from a normal state which has been attained, there is in children the possibility also of failing to grow up to the destined normal. Then there is the field, shared with the adult, in which a state of normality is mistakenly regarded as disease. Our professional counsel for perplexed parents will follow two broad paths: reassuring them about physical normality and restoring their emotional attitudes. The latter is the more insistent, elusive and time-consuming of the two tasks; we take it up usually during the processes of the former task in physical examination of the child. Hence the more we can see of normally growing babies and children with their parents, the more easily can parents confide their misgivings and relieve their tensions, and save us from wasted effort in the future. In the still longer view, these children, if skilfully brought up, will be easier parents for their own offspring in the next generation. It will be simpler to consider the emotions first, though noticing some physical matters in passing.

EMOTIONAL NORMALITY IN PARENTS AND FAMILIES

Doctors inevitably see a biased sample of the population, because the more unhappy and insecure people are likely to make the greater demands upon us. In hospital the sample is even more biased than that seen by family practitioners. The children's doctor endures every week a fascinating and concentrated dose of parents' fears, tangles and discontents. Many women enter matrimony and parenthood with queer tensions and arbitrary views, which they do not divulge to us readily. Many men display an equally queer lack of the tension of responsibility in sharing the care of their children. If 'fathercraft' were taught and learnt as vigorously as 'mothercraft', some homes would be more stable and some surgery hours shorter. Engaged couples, however, would be hard to enrol for joint instruction; and newly-weds are defeated by the race of time in making their home before the family arrive.

Young parents are often unsettled, their self-confidence undermined, and their satisfaction in parenthood blighted by the possessiveness of their own interfering mothers and mothers-in-law and the assertiveness of neighbours. Their doctors and nurses may be so busy that they can only hand out dogmatic rules and details, instead of giving the reasons for what they advise. These worried mothers never feel safe in handling and providing for their baby, and come to trouble their many advisers, including doctors, unnecessarily often. Clucking motherhood is a variant of emotionally insecure dependence, which wastes our time by too frequent calls. Older children are sometimes obviously ashamed and embarrassed at the fuss and flap their parents make.

THE FEAR OF PHTHISIS

Life for many parents is an uphill grudging struggle against menacing powers of fate. Foremost of these bogeys is the long crooked shadow of nineteenth-century phthisis, which blots the whole landscape of medical as well as lay thought. This morbid bias of mental association crops up with every simple childhood cough, every perspiring forehead during slumber, every transient lymph-node swelling, and many a pot-belly, colic or diarrhœa. Millions of units of vitamin D are given needlessly to fortify children against this supposed threat. Family doctors who keep in the surgery desk a bottle of acetone, a reel of adhesive tape and a tube of tuberculin jelly save themselves repeated visits, by eliminating tuberculosis from the differential diagnosis at the outset. The same spectre, if not that of Shakespeare's Cassius, is at the back of parents' discontent with lean, light-weight, wiry children, who are often the healthiest group of all. Food-forcing with its miserable conflicts also follows from tuberculophobia: consumption, however, is not fought with calories alone.

Parents set an abnormal valuation upon an x-ray of the coughing child's chest. With tears of relief they sigh, 'I feel so much better now I've SEEN that!', little realizing that it is the nasal sinus film which we are studying for clues more expectantly than the chest film. Among the coughs of childhood there is one important group which may be regarded almost as normal, yet by its aggressive noisiness it causes the keenest alarm. This is the deep-toned, paroxysmal, nocturnal, winter, 'dog-bark' cough, persisting for weeks after simple colds, in the absence of nose blockage or postnasal discharge. The consternation it causes, through disturbance of parents' sleep, impels us to exclude lung collapse and tuberculosis, by x-rays and skin tests: we can then pronounce it to be 'all bark and no bite', with a homely explanation that air passages which develop this dry tickle are more wholesome than the exudative tubes of other children.

THE SPECTRE OF MENTAL BREAKDOWN

The second dark emotional terror is that of mental breakdown. It causes alarm over the lively baby who needs less sleep than grandmother thinks

best, and the active schoolchild who fidgets when suppressed. Habit-spasms are an index of tension in parents rather than in offspring as a rule; and the child feels the unfairness of treatment directed by proxy at himself. Habit-spasms still lead too often to months of treatment with bed and sedatives, deprived of school, on a mistaken diagnosis of chorea.

SENTIMENTALITY

Sentimentality is a third fault which bedevils the parent-child relationship, mostly through 'smotherlove' which makes a bored, frustrated, dependent, helpless child. There are mothers who dramatize themselves as the guardian angel, ceaselessly unrelaxing to ward off germs, mishap and death from their precious charge. The pity is that they wear themselves out emotionally, and never begin to enjoy the child, who in turn can never enjoy his parents or himself.

Parents often exhaust themselves in house-proud drudging for bored children, who would have keenly enjoyed making a game of tidying and sharing in the household chores. The risks to the only child are well enough known: but the worst degree of this syndrome befalls the 'second-only' child, born a dozen years after a grown-up family, whose elderly parents fail to realize they have lost the resilience of their youth. Sentimentality causes much wastage of school time, through misjudgment of the risk of dry coughs and wheezing and lassitude. 'His HEALTH must come first!', they say. But, in fact, health as well as success in later life is more likely to be the reward of regularity than of absence from school.

LACK OF DISCIPLINE AND SCHOOL MISFITS

Discipline in many households is a 'hit or miss' haphazard matter, unregulated by policy, theory or consistency. Not enough parents regard themselves as concerned in the education of their children's character. An undisciplined child is as pitiable as a slack, vibrating, noisy machine-bearing, and suffers similar wear and tear.

Emotional health is jeopardized in the recurring grammar school 'misfits' which seem to be due to defective cultural background in the home. A mother gets at loggerheads with form-mistresses over homework. Or a father cares nothing about his child's progress beyond his own level of attainment, and gives no moral support or encouragement with lessons, sport or choice of career. The mental health of parents depends largely upon their personal relationships in marriage and in society, as in industry; and personal relations need cultivating for health. Our approach to these problems cannot but be governed by our own valuation of spiritual and religious principles in social life.

The most startling recent discovery in mental health has been summarized for the general reader by Bowlby ('Child Care and the Growth of Love', London, 1953). Studies in many countries show that a child's whole

personality and adaptation to life may be profoundly affected, and even irretrievably wrecked, through being deprived in infancy of mother-love and security. Not only may such a child be emotionally frozen and unable later to make successful social relationships, but his intellectual organization may also be arrested. Such deprived children grow up into problem adults, who reproduce disturbed and affectionless children in a self-perpetuating sequence. The picture is so grim that it demands hard thinking and resolute action to prevent this deprivation from occurring, to help parents fulfil their children's needs, to maintain the family intact, and to reconsider our handling of children who are unavoidably separated from their homes.

PHYSICAL ASPECTS OF NORMAL HEALTH

In childhood the range of the normal swings far wider than we are trained to think. In our undergraduate teaching time does not allow for explaining the limits of normality, and we have to be content with memorizing average mean figures. Hence it comes about that many normal appearances may be labelled as disease, and cause consternation to parents as well as misgiving to ourselves. The metabolism varies greatly from child to child, and in the same child at different ages. The appetite of some children is always frugal. Parents seldom realize how small a diet intake is sufficient for the toddler, who has only to gain 4 or 5 lb. (1.8 to 2.3 kg.) in a year. Unfortunately, protein and vitamin intake is neglected in the cut loaf and jam-pot regime of many homes. Children vary greatly in their natural mood of liveliness or placidity; and, commonly, parents are bewildered with their second child, who is endlessly active day and night by comparison with a vegetative first child some years ago. Negativism is the spice of life to the intelligent toddler, who realizes his powers of choice and his ability to devastate the mood of his anxious parents. The natural complexion of most children of our race is pale, and reassurance can be given by inspecting mucous membranes, even without blood counts. The sallowest of parents will come trembling with anxiety about the pallor of their brown-eyed child, whose hæmoglobin turns out to be fully normal.

PHYSIQUE

Children's physique has been shown to be influenced considerably by their birth weight and also by the stature of both parents: these two factors may indeed be directly related. Parents, however, commonly lose tranquillity for years through contrasting their slightly built fairy with the grosser offspring of neighbours. A problem here arises with the grading of children at school medical inspections. During the late war it was obviously important to watch vigilantly for undernutrition. The term 'general condition' has now replaced 'nutrition' in grading, but it still seems that a wrong emphasis may be given (especially to lay school committees) through confusing maximum with optimum, or quantity with quality. There is no reason, for instance, why an over-large child should be graded better than a slightly built child in the school health statistics.

A plea may be made for more remedial physical exercises and closer teamwork between teachers and physiotherapists for schoolchildren, to improve uncouth faults of posture and gait, including round shoulders and unnatural tilting of the pelvis, and the lordosis which lands numerous schoolgirls in corsets. At toddlers' clinics, however, nature might well be allowed freer play with some of the bow and bandy knees. The preventive archangel still tends to overwork the divinities which shape our ends in orthopædic operating theatres. Our education service has long arrears to make up in securing that all children become competent swimmers in their youth.

In athletics, teachers are up against inadequacy of playing space, and often also against the resistance of parents to healthy stripping for exercise. The family doctor sometimes has to umpire in these disputes. We are in the position to guide the stages of return of children to full activity after illness when some individual coaching of slack joints and muscles would sometimes accelerate restoration, and obviate prolonged absence.

SOME ADVANCES

The field for exercising our human interferiority complex has narrowed in recent years. The fate of the foreskin has been settled in favour of retaining it for almost every boy baby. Umbilical 'hernia' is rumoured now to close spontaneously even more regularly if we do not tinker with it by fuss and strapping: and the few which ultimately need operation would have been impossible to control even temporarily with appliances, and would have come to no harm by being left free during the first year. In this age of plastic pants for toddlers, mothers are set free from the chiding of babycraft experts who would have every infant house-trained before he can reason why. Children's tonsils have now passed almost entirely from the hands of the 'poachers' to the 'gamekeepers'; and this leaves our aural consultants free to give their time to the urgently important adenoid and sinus problems.

The brilliant success of diphtheria immunization in reducing the disease to negligible levels has now brought us to a dangerous national apathy to inoculation. Whooping-cough immunization has already brought clear rewards; and we now need a streamlined programme of combined diphtheria-pertussis-tetanus immunization which can be given early enough to prevent the disasters of whooping-cough in six-month-old babies. Air travel has brought smallpox back within striking distance of our community, making vaccination of all infants a requisite of sound health care.

REASSURING PARENTS

A large part of the work of family practitioners and of children's doctors in hospitals and clinics is to reassure parents, after examination, that the symptoms they dread are, in fact, not serious and even not significant. Some symptoms are proper to a state of health and are not necessarily disease. Normal children are entitled to certain normal pains, among which will be 'hunger contractions' or 'sinking feelings' before breakfast, awareness of

colon peristalsis, recurring 'stomachache' or intestinal colic, and some recurring limb pains which remain unexplained after carefully excluding subacute rheumatism. The embarrassment to a habitual nose-breather of a blocked nasal airway has to be felt to be believed. Not every wheeze during respiratory infections forebodes lifelong asthma; headaches do not always mean brain tumour. Bedwetting is more often a matter for homely management than for inscrutable psychiatric analysis.

Some parents appear to live in a continual daze of not realizing what has smitten them so unexpectedly. They were not forewarned of the amount of energy which would be required to satisfy all the quests and restless aspirations of childhood. The marriage vows included no covenant on their part to acquire the whole field of knowledge upon which children demand enlightenment, from the ethics of nose-blowing to the sex life of unicorns.

'THE DELICATE CHILD'

In the few years since the war we have moved far from the old concept of a 'delicate' constitution, which was supposed to require an Open-Air School life with periods of bed rest and extra nourishment. That concept was doubtless another edge of the shadow of tuberculosis, related to the rigorous sanatorium methods of treatment by fresh air and much food in a Spartan environment. Subnutrition was also a more important factor than nowadays. With the increase in consultative facilities it has been possible to return to ordinary schools many children who used to fill the open-air schools, which in some cases have become redundant and have been put to more pressing use. The 'delicate child' problem has now reduced itself practically to that of relapsing asthma, which commonly stays cured as long as the child is at a boarding school away from his home. Advertisements still carry soulful pictures of languid children purporting to be in trouble and so requiring special food supplements or beverages, after the style of the cartoons which exploit listlessness and insomnia in adults. In fact, however, the problem of such children would nearly always prove to be boredom, misunderstanding, dimwittedness or nattering at home, rather than shortage of some commodity that money can buy.

Children's hearts.—Much machinery is set clicking for innocent heart murmurs in children at all ages. The reason is that medical students are not taught to recognize specifically the common innocent murmur of childhood. Classical descriptions of this exist, but are not found in most of the standard undergraduate textbooks. The majority of benign murmurs fall into one broad recognizable group, about which any doctor should be able to say confidently, without seeking specialist confirmation, that it is innocent. The murmur is short and commences later than the first heart sound so that it can be recognized as a separate puff in mid-systole. It is low-pitched and often musical, creaking, grunting or hooting in quality. The murmur is loudest over mid-precordium and is not conducted widely. The characteristics of brevity, timing in mid-systole, and quality will positively dif-

ferentiate it in most cases from rheumatic valve scarring. In a minority, prolonged observation may be required, though without imposing interim restrictions on effort. So long as this very common murmur goes unrecognized we shall be in the wry position that the stethoscope at clinics and school inspections is more often an engine of despondency than of value. A highly circumstantial syndrome of breathlessness and blue lips grows up within a month of the mention of a murmur at school.

Migraine in childhood is best considered and handled as a vexatious variant of normal health. Contrary to some textbooks, it is a common condition even in the infant-school. It baffles us chiefly because we have been taught not to expect it in young children, because young children lack the vocabulary to describe their sensations, and because abdominal pain may be more prominent than headache. Mother and teachers will for years be exasperated over a supposed ne'er-do-well junior scholar with recurring pallor, prostration, stomachache and vomiting; and this, notwithstanding that father has had sharp migraine since adolescence. Once the mystery is solved, anxiety abates and discussion about open-air schools ceases.

CONCLUSION

If so much normality lurks concealed in human flesh, why is there not more enjoyment of it? The answer perhaps lies in the sphere of the juniormost archangel of health education, who has not yet attained professorial status. The medical curriculum has hitherto ignored public relations and propaganda and the art of imparting to patients such information as will guide their habits and form their outlook.

To plan for the future is not easy. We are beset by the doubt that sickens: are we sure our advice will stand the test of time? Will health education get into the hands of armchair cranks? Are the family doctor, medical officer of health and nurses agreed what they shall tell the public? How can adolescents be attracted at an age when they still have leisure to pursue health studies? How can we get the most needy stratum of society to see the value of heeding health advice? How can hospital doctors link up with family doctors to give sufficient explanations ('They never tell you anything at hospital')? How can we gear emotion with reason in the reading and thinking of the community? A benevolent Research Trust would find a fruitful field for co-operate study here.

I am indebted to Dr. J. Wood-Wilson, the West Riding County Medical Officer of Health, Professor Fraser Brockington and Professor R. S. Illingworth for the circumstances, guidance and teaching which have made these reflections possible.

THE DISCHARGING EAR IN GENERAL PRACTICE

By F. BOYES KORKIS, M.B., F.R.C.S., D.L.O.
Surgeon, Metropolitan Ear, Nose and Throat Hospital

NEVER before, in the long history of medicine, has it been possible for the general practitioner to treat successfully so many discharging ears than in the present era of chemo- and bio-therapy. With proper management the great majority of cases need never be referred for specialist treatment but there are others which will never respond to medical treatment and specialist intervention is indicated.

ARMAMENTARIUM

In order accurately to determine the diagnosis, certain instruments, which are few and simple and readily portable, are necessary. An efficient electric auriscope is required, to the head of which a small rubber bulb should always be attached. This is a great asset for, by its use, the movements of the drum may be observed and perforations can be distinguished readily from atrophic scars. If a perforation is present, a speculum fitting the external auditory meatus tightly is used. Negative pressure can be produced by the bulb to suck out any inflammatory secretions which may have accumulated in the middle ear, more thorough toilet of the ear thereby being possible. In the case of pin-point perforations, which are difficult to see, a bead of pus can be sucked out and the site of the perforation noted and a definite diagnosis of otitis media be made. Why greater use is not made of this simple device has always been a mystery to me, as nearly all modern auriscope heads are made with a metal tube on one side for the attachment of this bulb.

Before an opinion on the drum can be given it is necessary to carry out toilet of the canal and of the outer surfaces of the tympanic membrane, and for this purpose there is no better instrument than a Jobson Horne probe, which can be dressed with cotton-wool and used for gently mopping away pus and debris, whilst the ring-end of the probe is useful for removing cerumen. A nasal speculum should be available to examine the nose for the presence of pus, as no examination of the ear is complete until the nose and throat have been examined. The speculum which I find most useful is the Thudichum spring nasal speculum and two should be available: the small size for examining children, whilst the larger can be used for adults. The expanding nasal speculum, which is usually provided in electric diagnostic sets, is not a very satisfactory instrument to use. As one of the cardinal symptoms of ear disease is deafness, a tuning fork should always be used for determining the type of deafness present. In the case of suppurative disease of the middle ear, the tuning fork will reveal a typical middle-ear type of deafness; that is, the fork can be heard longer by bone conduction than by

air conduction; and if a vibrating fork is placed on the centre of the forehead, the patient appears to hear the fork on the affected side. The best tuning fork to use is one with a sounding base having a frequency of 512 double vibrations per second. An angled pair of dressing forceps, such as those of Tilley, is used for handling dressings and this completes the essential armamentarium.

AURAL TOILET

Before a differential diagnosis is possible it is essential that a clear view of the tympanic membrane be obtained. In the great majority of suppurating ears the meatus is filled with pus and debris and the first step is to clean the meatus and outer surface of the drum. Before any instrument is put into the canal, however, an inspection is made of the external ear, and the outer part of the external meatus. In this fashion, it is easy to see certain lesions such as furuncles and dermatitis of the pinna without the aid of an auriscope.

Of the two methods of cleaning the ears, namely the wet and the dry, the dry is by far the better. The patient is placed in a good light and the pinna is retracted backwards and upwards with the left hand. The Jobson Horne probe, which has been dressed with cotton-wool, is then used with a circular sweeping motion to clean out the canal. Periodical inspection with the auriscope is necessary, to ascertain whether the canal is clean. Desquamating epithelium should be removed from the outer surface of the drum, after which the auriscope is used again to note the condition of the tympanic membrane, when a diagnosis can be made between otitis externa (with an intact drum) and otitis media.

Aural toilet is also an essential preliminary to treatment, irrespective of whether the condition is otitis externa or otitis media.

OTOSCOPIC APPEARANCES

Otitis externa.—The outer surface of the drum, although perhaps reddened and covered with desquamating epithelium which is off-white in colour (and which has been removed by toilet), is seen to be intact, and moves freely.

Otitis media.—We are concerned in this article with cases in which there is active suppuration, and therefore there is a perforation present and the drum does not move. The perforation may be of any size but is in a central position in the tympanic membrane: i.e., it does not reach the periphery of the drumhead. It is often in the antero-inferior quadrant of the drum, and the type of discharge is muco-purulent and often profuse. This is the type which can be classified as a 'safe ear', as complications do not usually arise, and it is the type of infection which lends itself to domiciliary treatment.

Chronic mastoiditis.—When destruction of bone takes place in the middle ear the condition is no longer one of pure otitis media, and this term should not be applied when a diagnosis of mastoiditis is possible from the otoscopic appearances. Bony destruction occurs with two different types of lesions. In the first a cholesteatoma is present in the epitympanic region, and there is consequent destruction of the bone in the uppermost part of the tympanic

cavity including the head of the malleus. Perforation in such cases is therefore in the attic region and a small opening is seen either anteriorly or posteriorly in Shrapnell's membrane. The discharge is scanty, thick and foul-smelling. In the second, there is no cholesteatoma but bony necrosis takes place, usually in the region of the tympanic ring posteriorly. The perforation will then be situated in the periphery of the drum: i.e., it is marginal. It may be obscured by the presence of vascular granulations or perhaps by an aural polyp. The discharge is frankly purulent and scanty.

Both these types of discharging ear fall into the 'unsafe' category and should be referred without delay to an otologist, as surgical intervention may be necessary on account of complications which may ensue without warning, e.g., in the form of meningitis, brain abscess, lateral sinus thrombosis.

Labyrinthitis.—Labyrinthitis usually results from a neglected middle-ear suppuration and the otoscopic appearances are essentially the same as those enumerated above.

SAFE AND UNSAFE EARS

Apart from the otoscopic appearances, certain symptoms and signs may be encountered which are helpful in allocating a particular infection to one or other of these categories. Persistent headache in the temporal region of the skull suggests the possibility of irritation of the dura from an extradural abscess and should be looked on as a potentially unsafe ear. Likewise, when there is a history of recurrent pain deep in the ear, associated with a cessation of the aural discharge and relieved by the reappearance of the otorrhœa, bony necrosis should be suspected. Vertigo suggests labyrinthitis and calls for examination by an aural surgeon. A paralysis of the sixth cranial nerve indicates an infection in the tip of the petrous temporal bone (apical petrositis), whilst paresis of the facial nerve is brought about by pressure on the nerve by cholesteatoma. A cholesteatoma may also erode the labyrinth, when it is possible to elicit a positive fistula sign—vertigo and nystagmus on compression of the external auditory meatus on the affected side.

It is not uncommon in these days to see cases of so-called 'masked mastoiditis' in which none of the classical signs of acute mastoiditis are found. Instead, the aural discharge continues, or the patient remains deaf, despite adequate local treatment. The diagnosis in such cases is made on radiological grounds and requires reference to a radiological department.

The term 'safe' is, of course, only relative, for otorrhœa always carries with it potential risks if the discharge is allowed to persist.

FOCI OF INFECTION

The majority of cases of otitis externa are either associated with seborrhœa of the scalp or are secondary to a chronic infection of the middle ear or mastoid; in the case of children, foreign bodies in the external auditory meatus may be the responsible factor. As the condition will not respond unless the primary precipitating factor is treated or removed, careful ex-

amination should always be carried out to exclude these common factors.

In the case of middle-ear infection, the usual route of infection is *via* the Eustachian tube so that a thorough examination of the nose and naso-pharynx is called for. One should look for sinusitis, not only in adults but also in children, as an infection of the maxillary antra is common in young patients; likewise, many a discharging ear has been cured by the simple removal of enlarged and infected adenoids. These cases will naturally require reference to an ear, nose and throat department for surgical treatment.

HEARING

The aim of treatment should be not only to ensure a dry, healed ear but also to obtain the restoration of normal hearing if this is possible. Conservation of hearing has received too little consideration in the past. By adequate treatment of acute infections it should be possible to reduce considerably the number of patients who are handicapped by deafness as a result of chronic suppurative diseases of the ear. By early attention to chronic foci of infection, i.e., adenoids and sinusitis, the number of cases of recurrent otitis media, which may lead to permanent deafness, will be lessened.

The adequate treatment of the common infectious fevers of childhood by chemo- and bio-therapy has already had a noticeable effect in reducing the incidence of chronic suppurative middle-ear disease, which so often complicated them in the past. The acute mastoid is today a rarity, but a new subacute condition—'masked mastoiditis'—is with us; chronic mastoiditis is still encountered and, until the present generation of adults who were unlucky enough to develop their chronic discharging ears in the pre-chemotherapy era has been dealt with, will continue to be seen. Cases due to cholesteatoma will continue to arise from time to time, for the fundamental nature of cholesteatoma is still in doubt. By early diagnosis, however, while the lesion still occupies a limited area of the epitympanic space, conservative surgery is possible and offers the otologist the opportunity of conserving hearing by avoiding a radical mastoid operation. No time should therefore be lost in diagnosing cholesteatoma, or wasted by instituting, or persisting in, useless medical treatment.

Indeed, all 'unsafe' ears, once diagnosed as such, should be given the earliest opportunity of thorough investigation, not only to avoid complications but also to allow the patient to retain the maximum amount of hearing.

PRINCIPLES OF TREATMENT

Aural toilet and dressings.—Regular toilet is indicated whenever there is pus in the canal. It is good practice to place a 5-inch length of dry ribbon gauze wick, $\frac{1}{2}$-inch in width, in the meatus when it has been cleaned. In the active stage of suppuration this procedure is repeated once daily, and perhaps more often if the discharge is profuse. This treatment should be carried out personally, if circumstances permit, as patients and their relatives cannot be expected to carry out a satisfactory toilet of the whole meatus down to the

drum. Herein lies the secret of success. Many 'safe' ears which have been discharging for years clear up quickly and completely on this simple regime without the aid of any other treatment.

Sometimes, however, a local medicament on the wick is helpful. When the meatus is very swollen and painful, 10 per cent. ichthyol in glycerin is a soothing application which has stood the test of time. For desquamative otitis externa a 2 per cent. aqueous solution of lead subacetate is helpful; if the infecting organism is *Ps. æruginosa*, 2 per cent. acetic acid is useful. Owing to the risks of sensitization of the tissues of the external auditory meatus and surrounding areas, it is wise to avoid the local use of antibiotics and chemotherapeutic agents. When an otorrhœa has failed to respond to simple toilet, however, 10 per cent. chloramphenicol in propylene glycol may be used on the wick. If it is going to benefit the infection it will produce dramatic improvement quickly; if there has been no favourable response after five days, its use should be abandoned. In cases which respond well this treatment should not be continued for more than a week, as it is after this time that trouble occurs from local allergic reactions to the drug.

Auristillæ.—Aural drops have gained immense popularity with practitioners and patients alike but it is difficult to see why, apart from the psychological effect of putting something into the diseased area. Aural drops are prescribed for two main therapeutic reasons: to lessen pain and to combat infection. Both these objectives, however, are more certainly obtained by other means: the first by local heat and anodynes, the second by parenteral chemo- or bio-therapy. When they are used, not only is toilet neglected but local sensitization may ensue with certain preparations (e.g. chloramphenicol), and in my view the most certain way of converting an acute otorrhœa into a chronic one is to send the patient away with a prescription for a large bottle of aural drops. One constantly sees cases in which an otorrhœa ceases after stopping the use of the aural drops and instituting simple dry toilet. The moral therefore is to avoid the use of auristillæ.

Aural insufflations.—Unlike drops, powders for aural insufflation serve a useful purpose but again caution is needed in their use. If an otorrhœa is at all profuse, powders will not help but are most useful in the case of a chronic middle-ear infection which remains moist, the discharge being mucoid in type and scanty in quantity. They are also of great help in the after-treatment of radical mastoid and fenestration cavities. Certain powders, especially the sulphonamides, may cause local tissue reactions; moreover, the powder often consolidates to form a concrete-like mass in the meatus. Such powders therefore should never be used.

The most useful general-purpose powder is insufflation of iodine and boric acid, B.P.C. This does not tend to set in a hard mass and can be wiped away with ease. Another powder which may help a resistant case is chloramphenicol, the capsule containing the powder being perforated to allow its insufflation into the ear. This method makes for economy in the use of an expensive drug and is to be preferred to a solution of chloramphenicol in

propylene glycol. Oxytetracyline ('terramycin') powder gives promise of being useful, especially for drying up moist operation cavities in the temporal bone, but it is too early yet to say whether it has any particular advantages or disadvantages over chloramphenicol.

Systemic treatment.—To control the invading bacteria, chemotherapeutic or antibiotic agents are ordered in acute cases, for the organisms are then likely to be sensitive to these agents if given systemically. As in general practice it is impractical to carry out routine bacteriological sensitivity tests, one has to assume that the particular drug chosen will be effective against streptococci, staphylococci, and pneumococci which are the usual primary invaders of the middle and outer ears in acute infections. Moreover, valuable time is wasted while the results of such investigations are awaited. The sound working rule is: get in quickly with an adequate dose of the preparation chosen. In general, for the sake of convenience, the sulphonamides are most useful in adults, whilst for young children one of the preparations of penicillin for oral administration is adequate and saves the distress of repeated injections. If desired, ordinary penicillin may, of course, be given to both adults and children. The dosage should be such as to give an adequate blood level in as short a time as possible, and this effective blood-level concentration must be maintained for at least five days, even though the ear may appear to have settled down in the meantime. By adopting this practice there should be less chance of the patient developing a 'masked' mastoiditis, or other complication, as the infection is then fully controlled and not merely suppressed. Naturally, in severe cases a much longer course of treatment is required, and the clinical condition of the patient should be the determining factor. When the ear has completely settled down clinically, the administration should be continued for a further two or three days.

In chronic infections the original bacteria are often supplanted by secondary invaders (commonly by *Ps. æruginosa* and *Proteus*), which are not likely to respond to sulphonamides or penicillin. In such cases it is wise to take a swab from the ear and send it for full bacteriological investigation, including sensitivity tests. No antibiotic should be prescribed until the sensitivity is known, as chronic cases come to no harm by waiting a few days. In the meantime, regular local treatment may well clear up the ear and antibiotic therapy may not be required at all.

Ancillary treatment.—For the control of pain, dry heat is preferable to wet, and in the home the hot-water bottle and electric radiator are readily available sources of dry warmth. In addition, anodynes should be prescribed. It must never be forgotten that rest is one of the most important factors in treatment, and in really acute cases bed rest should be advised.

CONCLUSION

The views expressed are personal ones, but I have found them to offer a useful working guide for the majority of infections of the ear with which the practitioner is confronted.

GENERAL PRACTITIONERS' FORUM

TREATMENT OF NOCTURNAL ENURESIS WITH ENTERIC-COATED AMPHETAMINE

By GUY DAYNES, M.R.C.S., L.R.C.P., D.C.H.
Hove

WHILE treating cases of nocturnal enuresis with standard amphetamine tablets I commonly found that the patients remained dry for the first part of the night, only to wet their beds between four and six o'clock in the morning, when the main effect of the amphetamine had worn off. I therefore had some enteric-coated amphetamine tablets (5 mg.) made up, and used these in conjunction with the plain amphetamine tablets. The results proved extremely satisfactory, particularly in those children over the age of twelve who were still suffering from this distressing complaint at that age.

INDICATIONS

Children over the age of seven who were persistently wetting their bed at night, and whose sleep seemed abnormally deep, responded best.

DOSAGE AND METHOD OF ADMINISTRATION

The starting dose is 5 mg. of ordinary amphetamine and 5 mg. of enteric-coated amphetamine. This dosage is increased every second or third day until the wetting is controlled or the patient spends a wakeful night. If the wetting is controlled, then the dose is stabilized at that level. If a wakeful night occurs the dosage is reduced, depending upon *when* the wakefulness occurred—difficulty in getting off to sleep or early wakefulness indicates excessive ordinary amphetamine, whereas waking in the early hours of the morning calls for reduction of the enteric-coated dose. The commonly effective dosage is 10 to 15 mg. of each type of tablet; sometimes more enteric-coated than ordinary tablets are required, and less often, the other way round.

CONTINUATION THERAPY

Once an effective dosage has been found this should be kept up for six months to a year, although during this time some patients seem to require slight reductions in dosage, in order to avoid wakeful nights. Provided the dose is right, the patients have just as refreshing a sleep as they do without any tablets at all, and many will say *more* truly refreshing than they can remember having had before. Many patients find that they require higher

dosage if they have had a very exciting day or are overtired, and conversely they require less at times when peace reigns. Children over twelve can soon learn to regulate their own dosage within prescribed limits.

ILLUSTRATIVE CASES

An intelligent boy (N.J.), aged 19, had wet his bed all his life and seldom had more than two or three dry nights a week. He had been to a number of specialists when he was younger, and two years before he was first seen had been in hospital for three weeks when amphetamine treatment had been tried. It only succeeded in keeping him dry during the first part of the night, after which he was able to sleep only to find himself wet in the morning. His sleep was always very deep, and latterly he had had to have three alarm clocks timed to go off one after the other in order to wake him in the morning in time for work. He was loath to try amphetamine treatment again because of his unfortunate experience in hospital, but finally was persuaded to 'take a chance on it'. His dose was worked up to 15 mg. of plain amphetamine and 15 mg. of enteric-coated, at which point he became dry and found that his sleeping was much lighter, only one alarm clock being necessary to wake him. A week or two later he became wakeful in the early part of the night, and accordingly reduced the plain amphetamine to 10 mg., keeping the enteric-coated at 15 mg.

Now, 18 months after initiating treatment, he requires 10 mg. of each as a maximum on 'tired' nights only, and wetting is a thing of the past. A few weeks ago he wrote that he had been able to go away and stay with friends for the first time in his life.

A girl (P.D.), aged 15, presented with a history of persistent bed-wetting all her life, one dry night a week being the best she could manage. She was treated with ordinary amphetamine at first but this was of little permanent avail, although there was a temporary improvement for the first few days. Later she began to be wakeful in the early part of the night and wetted in the mornings when her sleep became very deep. She made a very satisfactory response to the combined therapy described above and in six months became quite dry as long as she took the tablets. Now, two years after starting treatment, she has been able to stop the amphetamine altogether, and is quite cured of nocturnal enuresis.

CONCLUSION

Enteric-coated amphetamine tablets used in conjunction with plain amphetamine can be of great value in some cases of persistent nocturnal enuresis. Nevertheless, reliance should not be placed on this form of therapy alone, for psychotherapy will always have a part to play as well, if only in mitigating the psychical trauma to the child caused by the consequences of the condition itself.

THE CHOICE OF PLASMA SUBSTITUTE

By E. J. FAIRLIE, M.B., B.S., D.R.C.O.G.
York

ALTHOUGH the use of plasma substitutes in this country is mainly the concern of those in hospital practice, they are also the concern of every practitioner who undertakes obstetrics, for in 1952, in England and Wales, there

were at least 34 maternal deaths as a result of post-partum hæmorrhage. A general practitioner attending such an emergency can easily have with him the means of restoring to normal the blood pressure of a pulseless and unconscious patient in the interval taken for the 'flying squad' to arrive. National blood transfusion sets and bottles of plasma substitutes are readily available, and they will keep for many months.

Many practitioners would consider the administration of blood which has not been properly cross-matched (or Group O Rh-negative blood when the blood group has not been determined) to be justifiable in circumstances such as severe post-partum hæmorrhage, as the chance of incompatibility is remote. The use of plasma would obviate any such risk, but the possibility that it might cause infective hepatitis weighs heavily against its regular use. There are three substitutes for plasma available, and it is proposed to discuss their relative merits.

Dextran is a naturally occurring gum manufactured on a large scale by the fermentation of sucrose. It is usually prepared as a 6 per cent. solution in normal saline.

Polyvinyl pyrrolidone, or *polyvidone*, is a synthetic substance made by polymerization of vinylpyrrolidone. It is sold in this country under the name of 'plasmosan' as a 3.5 per cent. aqueous solution, with electrolytes in the same proportion as in plasma.

Acacia is a gum exuded from the stem and branches of a number of species of Acacia. Injection of sodium chloride and acacia, B.P. 1932, (gum-saline) was introduced thirty-five years ago by Bayliss as a means of restoring a depleted blood volume. Its use was never generally accepted, and at times has been severely criticized, but recently it has been described as a safe and efficient fluid which has stood the test of time (Gibberd, 1951). It was perhaps unfortunate that gum-saline was introduced at a time when intravenous therapy was in its infancy, for it was customary to make up the solution in the hospital dispensary; accordingly, with little accurate control over its preparation, reactions following its use were fairly common. Even so, between 1926 and 1932, 3000 intravenous infusions of gum-saline were given at the Mayo Clinic and only one unfavourable reaction was described (Maytum, 1932). Reactions with gum-saline are practically unknown today if a reliable preparation is used. The other main criticism of acacia is that it is known to be stored in the liver, spleen and kidneys.

PROPERTIES OF MACROMOLECULAR SUBSTANCES USED AS PLASMA SUBSTITUTES

To be effective as a plasma substitute the substance in solution (dextran, polyvidone, or acacia) must have a molecular weight near to that of albumin (i.e. 72,000). Acacia, in its natural state, consists of a range of molecular weights with an average approximating that of albumin. In the first stage of their manufacture dextran and polyvidone consist of molecules too large to

be used as plasma substitutes; these are broken down by a process of depolymerization into a range of molecular weights somewhat similar to that of acacia. It is generally recognized that all such macromolecular substances of suitable size to be used as plasma substitutes behave in a remarkably similar manner to one another when injected into the circulation (Mannix, 1947). Raised E.S.R. and rouleaux formation in the blood are well known in using dextran but are characteristic of the other plasma substitutes. Also, with all such substances, the smaller molecules are known to be excreted rapidly in the urine, and the larger molecules are retained in the circulation until they are stored in the reticulo-endothelium, giving histological appearances resembling lipoid storage disease. Unfortunately, it is the larger molecules which give a sustained effect as plasma expanders. It would seem that with the administration of small amounts of macromolecular substances, storage in the reticulo-endothelium is not obvious. In the case of dextran, Bull *et al.* (1949) found no evidence of storage after administration of small amounts to experimental animals, but with larger doses considerable damage and reaction in the spleen, liver and kidneys have been described (Turner *et al.*, 1949). It is important to note that much of the experimental work upon which acacia has been criticized consisted in the administration of large doses of acacia to animals over long periods (Andersch and Gibson, 1934), and that it was in cases of nephrosis in which frequent large doses had been given in an attempt to replace the low plasma proteins that post-mortem evidence of storage of acacia in the tissues was found. This use for acacia has probably been abandoned.

Although there is no obvious evidence of storage of these macromolecular substances in the doses used in augmenting a depleted blood volume (i.e., not more than 1 litre) this possibility must always be borne in mind as a potential danger, and their administration should be stopped at the earliest opportunity. It is also important to remember to take a sample of blood before giving a plasma substitute, as the effect of these substances on the red cells will complicate the cross-matching of blood so long as they remain in the circulation.

FATE OF DEXTRAN AND POLYVIDONE

The mode of excretion of polyvidone is of some considerable importance as it is unlikely to be metabolized in the body. The manufacturers of 'plasmosan' claim that polyvidone molecules of all molecular weights present in the solution are capable of being excreted by the normal kidney. They give no published evidence to support this claim which is difficult to correlate with the sustained effect which 'plasmosan' exerts as a plasma expander. There is no conclusive evidence as to the fate of dextran in the body. It is known that the larger molecules which are retained in the circulation are eventually stored in the reticulo-endothelium, and it is thought that they are completely metabolized within a few weeks. Dextran and acacia are both polysaccharides

of the same empirical formula $(C_6H_{10}O_5)_n$. It would seem possible that if dextran is capable of metabolism so also is acacia.

Recently, the manufacturers of dextran and polyvidone have suggested the use of concentrated solutions of these substances as a means of relieving the œdema of nephrosis and for treating pre-eclampsia and eclampsia. It has already been pointed out that the use of acacia for this purpose has probably been abandoned. The use of a substance potentially injurious to liver and kidneys should surely be condemned in cases in which damage already exists in these organs.

PRESSOR EFFECT OF PLASMA SUBSTITUTES

Plasma substitutes have their main action by virtue of the colloidal osmotic pressure which they exert, and it is usually supposed that they are rather poor substitutes for cross-matched blood. In treating a patient suffering from circulatory collapse due to blood loss, there are two points worth noting:—(1) By ordinary intravenous technique a plasma substitute can be made to flow appreciably faster than blood; (2) the rapidity of rise of blood pressure following administration of a plasma substitute is much greater than would be expected with administration of a similar volume of blood. Furthermore, it has been noticed that failure of blood pressure to return to normal following replacement of the same volume of blood as that lost has been remedied by the administration of a small volume of acacia or dextran (Wilkinson, 1951). The mechanism of this pressor effect is not understood, but in the case of polyvidone it has been suggested that a reversible combination with plasma globulins and globulins in the cell wall reduces the capillary permeability, in addition to exerting a colloidal osmotic pressure effect.

CONCLUSION

There is little to suggest that the use of the costlier dextran or polyvidone as a plasma substitute is preferable to the use of acacia. Polyvidone would seem to be the least desirable preparation in view of the fact that it is unlikely to be metabolized in the body. Further work on dextran might well be carried out along with experiments on acacia, as the two substances have a close resemblance.

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ANTON CHEKHOV

GENERAL PRACTITIONER AND PIONEER IN SOCIAL MEDICINE

By J. TODD, M.B., D.P.M.
Assistant Psychiatrist, Littlemore Hospital, Nr. Oxford

'Medicine is my lawful wife and literature my mistress. When I am bored with one, I spend the night with the other'.—Anton Chekhov.

THERE appears in a well-known book, 'Great Short Stories of the World', the following statement: 'Chekhov stands out as one of the greatest short story writers of the world. Although he received an M.D. degree, he never practised medicine, but devoted himself to writing'. This statement is inaccurate and does no justice to a man who dedicated many years of his short life to the active practice of medicine. Chekhov was not only a great writer, but also a talented doctor whose forte was general practice. Long after his literary triumphs had spread his fame throughout Russia, he continued to work as a general practitioner, until the ravages of consumption robbed him of the necessary strength to carry on. Chekhov's contributions to medicine, however, were by no means confined to his work as a general practitioner. Indeed, he showed himself to be as ubiquitous and versatile in his medical, as in his literary, interests. In this respect, it is instructive to compare Anton Chekhov with the German poet and dramatist, Friedrich Schiller, who made scant use of his medical training.

Anton Chekhov in 1899

EARLY DAYS

Anton Pavlovich Chekhov was born on January 17, 1860, in the South Russian town of Taganrog. His father, Paul Chekhov, kept a small shop in the town. The Chekhovs were originally of peasant stock; the grandfather,

born a serf, had bought the freedom of his family at 700 roubles a head. By degrees, the Chekhov family had become elevated in social status to the lower ranks of the bourgeoisie. As a scholar, Anton, whose head was noticeably large, was not particularly distinguished. Indeed, he was placed only eleventh out of twenty-three in the passing-out class. There can be little doubt, however, that his school work suffered grievously from the selfish attitude of his puritanical and intolerant father who monopolized his out-of-school hours with tedious duties in church and shop. When only 16 years of age, Anton had to fend for himself and earn his daily bread and butter, but he managed somehow to make ends meet until 1879, when, having passed his matriculation, he entered the Faculty of Medicine at Moscow University. By dint of 'hack' writing, which went very much against his grain, he supported himself during the difficult years as a medical student. He passed the final examinations for his medical degree in May, 1884, and lost no time in beginning his work as a doctor.

'I AM A DOCTOR'

Acting as locum tenens, he took on the duties of Director of the Zvenigorad Zemstvo Hospital, near Voskressensk. For several months he attended the patients in the hospital, appeared at inquests, and gave evidence in Court on medical matters. During the next six years he strove arduously to satisfy the rival claims of literature and medicine; Chekhov, the author, ever drawing inspiration from Chekhov, the doctor. His letters, in these early years, contain many references to his work as a doctor. In 1885, he wrote to an uncle excusing himself for not settling down in his native Taganrog:—

'As a doctor I should have grown slack in Taganrog and forgotten my medicine but in Moscow a doctor has no time to go to the club and play cards. As a writer, I am no use except in Moscow or Petersburg. My medical work is progressing little by little. I go on steadily treating patients. Every day I have to spend more than a rouble on cabs. I have a lot of friends and therefore many patients. Half of them I have to treat for nothing, but the other half pay me three or five roubles a visit . . .'

In 1886, a letter to his friend, confidant, and publisher, Souvorin, contains a reference to his medical activities:—

'I am a doctor and practise medicine . . . I cannot guarantee that tomorrow I won't be dragged from my table for a whole day'. In the same year he wrote to Grigorovich: 'I am a doctor and am steeped ear-deep in my medicine'.

In 1888, under pressure from Souvorin to give up medicine in favour of authorship, he wrote:—

'. . . you advise me not to hunt after two hares at once and not to think of practising medicine. I do not know why one should not hunt two hares, even in the literal sense. If there are hounds, then why not hunt? In all probability it's the hounds (in the metaphorical sense now) that I haven't got, but I feel more contented when I remember that I have two professions and not one. Medicine is my lawful wife and literature my mistress. When I am bored with one, I spend the night with the other. Though this is irregular it is not monotonous, and, besides, neither really loses anything through my infidelity. If I had not my medical work I could hardly give my leisure and my spare thoughts to literature . . .'

In 1888, Chekhov, in need of a well-earned rest, arrived for a holiday at the lovely country district of Soumy. Nevertheless, he was soon assiduously at work helping the local doctor, a woman, in her onerous duties. The impression his worthy colleague made upon him is recorded in a letter to Souvorin:

'Patients are a real torture to her, and she is almost morbidly scrupulous with them. At consultations we always disagree; I bring good tidings where she sees death, and I double the doses which she prescribes. But where death is obvious and inevitable, then my doctor feels in an altogether unprofessional way. Once I was attending patients with her in a certain medical centre; a young peasant woman came with a malignant tumour in the glands of her neck and at the back of her head. The tumour had spread so far that a cure was unthinkable. And just because the woman was at present feeling no pain, but would in six months die in agony, my doctor looked at her in a deeply guilty way, as if apologising for her own health and ashamed that medical science was helpless'.

It is at once evident that Chekhov admired this colleague more for the gentleness of her personality than for her abilities as a doctor. While allowing that women could make good doctors, he cast doubt on their potentialities as research workers: 'In all the thirty years of their existence women doctors (excellent doctors!) have not provided a single serious medical dissertation, from which it is clear that in the sphere of creative activity they don't count'.

SAGHALIEN ISLAND

In 1890, Chekhov surprised his friends by announcing his intention of visiting the notorious prison settlement on Saghalien Island, to investigate the living conditions endured by the deported convicts. The journey was undertaken by Chekhov to pay his 'debt to medicine', as he was conscious of a sense of guilt connected with his inability to practise regularly as a doctor. It was his intention to use his experiences in Saghalien Island to write a thesis of scientific importance. The journey exposed him (already suffering from consumption) to great hardship and privation as it involved two months of travel under primitive conditions. At least half this time had to be spent in horse-drawn vehicles over some of the worst roads in the world. During the journey, he was nearly drowned while crossing the Tom, narrowly escaped injury in a collision with a group of troikas, and half-starved by a shortage of foodstuffs. However, he held to his self-appointed task with admirable courage and Spartan fortitude.

His book 'Saghalien Island' contains a detailed description of the living conditions endured by the convicts. It is mainly a contribution to sociology, but an important chapter is devoted to the morbidity and mortality of the island's population. Chekhov found venereal disease rife in the island population, and the local hospital deplorably equipped. The book produced a sensation throughout Russia, and opened the people's eyes to the true state of affairs in the penal settlement. Official notice was taken of his book, largely because Chekhov was a doctor, a fact-finding mission being dispatched to Saghalien by the Department of Prison Administration. As a result, Chekhov's findings were fully confirmed. 'Saghalien Island', however, was deliberately ignored by the literary world as it was suspected that

Chekhov had undertaken the journey to Saghalien for the purpose of self-advertisement. After Chekhov's death the famous scientist, Professor Mikhail Chlenov, expressed the opinion that 'Saghalien Island' 'would serve as a model for works of this nature, when a department of ethnographical medicine, which we need so much, is opened up'. A fitting, if belated, tribute to a work that constitutes a definite contribution to human welfare.

THE COUNTRY PRACTITIONER

Soon after his return from Saghalien, Chekhov purchased a farm in the village of Melikhovo, about 50 miles from Moscow, where he once again settled down to the hectic life of a general practitioner. At that time doctors were scarce in Russia, so that before long ailing peasants began to assemble outside their new neighbour's gate. In addition, he was elected a member of the Sanitary Council in the nearest large town, and put in sole charge of anti-cholera precautions in an area covering 25 villages. In attending to his medical duties, Dr. Chekhov, himself a sick man, rose uncomplainingly from his bed at any hour of the night, when called upon to help a patient in some distant village or outlying farm. On these occasions, he was obliged to use a horse-drawn carriage to negotiate the appalling roads, as often as not buried in snow, and often hidden from view by impenetrable darkness. The exacting nature of Chekhov's medical commitments at Melikhovo is apparent from the letters he sent to Souvorin in 1892, and 1893, respectively. The letter written in 1892 refers briefly to his medical work:—

'There is to be a Zemstvo Council meeting on 20th October. It is intended (I read this in the account) to thank me for organizing the district. From August to 15th October, I had 500 patients registered on my cards; altogether I have probably attended over a thousand cases. My district was lucky in having a doctor, an assistant, and two splendid wards; patients came here and patients were attended at their houses; accounts were sent to the Health Bureau but only Rbls. 110.76 Cop. were spent. The lion's share of expenses I shouldered upon my manufacturing neighbours, who paid for what the Zemstvo had to pay . . .'

The letter written in 1893 refers to the non-appearance of the expected cholera epidemic, in anticipation of which, Chekhov had laid the most careful plans:—

'During the summer I remained in one spot, treated patients, visited patients, waited for the cholera. I received a thousand patients and wasted a lot of time, but there was no cholera. I wrote nothing, and all the time spared from medicine I amused myself, read, or arranged my cumbrous material on Saghalien . . .'

According to his sister, Maria Pavlovna Chekhov, who helped him as a trained nurse, her brother attended more than a thousand sick peasants a year in his own house, supplied them with medicine, and charged them nothing for his services. It seems, however, that Chekhov would occasionally accept some such gift as a pig from a grateful patient. His active practice of medicine in the Melikhovo district was terminated by an exacerbation of the pulmonary tuberculosis to which he ultimately succumbed.

In 1944, a museum was opened at Melikhovo in Chekhov's honour. At the

opening ceremony, an old peasant made a speech in which he tendered a public apology on behalf of himself and his fellow-villagers for the insistent demands they had made on Chekhov's services as a doctor, thus, perhaps, accelerating his death.

THE 'CHRONICLE OF SURGERY'

Although Chekhov's failing health eventually prevented him from actively practising medicine, it did not stop him from serving medicine in other important ways. In 1895, he rushed to the assistance of the *Chronicle of Surgery*, threatened with extinction by the high cost of production. In a letter to Souvorin, he deplores the plight of the journal, and gives an account of the tremendous efforts he had made on its behalf. The letter ends with an impassioned appeal for help and advice:—

'Will you instruct me? In order to save the journal, I am ready to go anywhere and stand in anyone's antechamber. If I succeed, it will give me great relief and pleasure, for to save a surgical journal is as useful a work as to perform twenty thousand successful operations. Anyhow, advise me what to do . . .'

Fortunately, Chekhov's efforts were not in vain and the journal was saved.

Increasing ill health forced Chekhov to spend the last few years of his short life wandering from one resort to another, in pursuit of the health that was never to return. In 1898, having at last given way to the dictates of his health, he forsook his beloved Melikhovo for the seaside resort at Yalta in the Crimea. Nevertheless, he continued to assist the sick in whatever ways remained open to him. For example, moved to compassion by the desperate plight of the destitute consumptives to be found in Yalta, he was soon at work organizing subscriptions from all over Russia, for the equipment of a new sanatorium. Chekhov spent the winter of 1901 in Nice, as he was no longer able to endure the rigours of the Russian winter. While in Nice, he succeeded in persuading a Miss Vassiliev to donate the necessary money for the building of a new skin hospital. In a letter to his friend, Chlenov, describing the steps taken to raise the money for the new hospital, Chekhov, with characteristic modesty, ends by asking his friend to refrain from making public his (Chekhov's) own part in the affair.

DEFENCE OF DOCTORS

Chekhov sometimes poked fun at doctors in his plays, but sprang to their defence in real life. Thus, having rebuked Souvorin for what he considered to be unfair criticism of the doctor attending Nicolay Chekhov (Anton's brother) in his last illness, he seized the opportunity to defend doctors:—

'Speaking of Nicolay and of the doctor who attended him, you emphasize that "all this is done without love, without self-sacrifice, even in regard to trifling inconveniences". You are right to say that of people generally, but what would you have the doctors do? If, as your nurse says, "the inside has burst", what can a doctor do, even if he desires to give his life to the patient? As a rule, while the family, the relatives, and the servants are taking "every step" and exerting their

greatest efforts, the doctor sits and looks like a fool, his hands folded, gloomily ashamed of himself and of his science, and trying to preserve his air of external calmness . . . Doctors have disgusting days and hours; God forbid anyone experiencing them. It is true that ignoramuses and sneaks are not a rarity among doctors any more than among writers, engineers, people generally, but those disgusting hours and days of which I am speaking fall only to doctors, and because of that, in fairness, much should be forgiven them'.

Chekhov greatly admired and revered Tolstoy as a man. Indeed, when Tolstoy was seriously ill in 1901, he had written: 'I fear Tolstoy's death; if he were to die it would leave a great empty place in my life'. Nevertheless, he did not hesitate to attack the famous author of 'War and Peace' for his hostile attitude to doctors, accusing him of being 'soaked through and through with hatred for medicine'.

DOCTORS IN HIS WRITINGS

Chekhov often wrote about doctors (usually general practitioners) in his short stories and plays. 'Ward No. 6', perhaps the most popular of his short stories, seems to combine a satirical attack on Tolstoy's negativistic philosophy with an exposé of the deplorable conditions prevailing in Russian provincial hospitals. Chekhov's doctor-characters were often used as convenient symbols with which to air his personal opinions. Thus, he makes use of Doctor Blagovo in 'My Life' to refute the philosophy of Misail, and Doctor Korolyov in 'A Doctor's Visit' to expose and criticize factory conditions. It is of interest that many authorities see in Doctor Astrov, a country practitioner in the play 'Uncle Vanya', the personification and embodiment of Chekhov's own ideals.

Notwithstanding his prolific production of literary works, his strenuous labours as a general practitioner, and his peregrinations throughout Russia, Chekhov found time to write an important and impressive work, 'The History of Medicine in Russia'.

EPILOGUE

The pride Chekhov took in his profession is shown, rather touchingly, by an incident arising out of the completion of his wife's passport. In January, 1900, he had been elected an honorary member of the Academy of Sciences, in those days the highest honour a writer could obtain. One day, when he was about to make an entry in his wife's passport, he turned to her and said: 'At first I wanted to make you the wife of an Honorary Academician, but then I decided that it was far pleasanter to be the wife of a doctor'. He then wrote 'wife of a doctor' in the passport.

When Anton Chekhov died at the age of 44 years, on July 2, 1904, at Badenweiler, Germany, the world lost a great author, and Russia a great doctor.

In the compilation of the data of this article, I have consulted several works, but in particular, valuable information was obtained from: 'The Life and Letters of Anton Tchekhov', translated and edited by S. S. Koteliansky and Philip Tomlinson; and 'Chekhov', edited by Ronald Hingley.

CURRENT THERAPEUTICS

LXXXIII—THE USE OF THE ANTITHYROID DRUGS IN THE TREATMENT OF HYPERTHYROIDISM

By SAMUEL P. ASPER, Jr., M.D.
Associate Professor of Medicine, The Johns Hopkins University School of Medicine; Physician, The Johns Hopkins Hospital, Baltimore, Maryland

A new approach to the therapy of disorders of endocrine hyperfunction, standing apart from ablation but gaining similar benefit, was marked by the introduction of thiourea or thiouracil in the treatment of hyperthyroidism (Astwood, 1943). In this instance a chemical agent produces amelioration of the disease by inhibiting excess hormone production. Thiourea and thiouracil and certain other compounds of both related and unrelated chemical configuration prevent the synthesis of thyroxine by the thyroid gland. These compounds have come therefore to be known as the 'antithyroid' drugs. The administration of one of these compounds in sufficient dosage to a thyrotoxic subject results in a gradual lowering of the metabolism to normal and, if such dosage is continued, to subnormal levels. Clinical proof that thiourea and related compounds act to prevent hormone production, and not to interfere with the action of the hormone itself, is shown simply by the fact that if they are administered to athyreotic patients maintained in euthyroidism with desiccated thyroid no lowering of metabolism can be achieved.

Astwood's discovery, so clearly related in his Harvey Lecture (1945), has been recognized by physicians the world over as an important contribution to thyroidology, for not only did his basic observation permit many original and fundamental studies in thyroid physiology, but it also opened a new avenue to the treatment of thyrotoxicosis. The clinical experience of the past ten years with these drugs now allows some definition of their advantages and disadvantages. Whilst differences of opinion may be held by various observers as to certain aspects of therapy with these drugs, no-one questions their great therapeutic value.

A large number of compounds has received clinical trial. Among these are thiourea, thiouracil, methyl- ethyl- and propyl-thiouracil, thiobarbital, methimazole*, and carbimazole†. In Great Britain methylthiouracil and carbimazole have been extensively tested, whereas in the United States propylthiouracil and methimazole have received the greater attention. Save perhaps for differences in incidence of toxicity, no single drug appears to hold advantage over the others.

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*Methimazole is 1-methyl-2-mercaptoimidazole. It is also known as 'mercazole' in Great Britain and 'tapazole' in the United States.

†Carbimazole is 2-carbethoxythio-1-methylglyoxaline. It is also known as 'neomercazole' in Great Britain.

DOSAGE

An important consideration in the use of antithyroid drugs is dosage, for with insufficient dosage little or no therapeutic benefit will accrue. The severity of thyrotoxicosis and the size of the goitre may govern to some extent the dosage for initial therapy. On the other hand, since effective dosage levels have been determined for each of the most extensively studied drugs and, moreover, since the incidence of toxic reactions is not greater with increments in dosage which remain in the accepted therapeutic range, it is advisable always to give initial therapy at a dosage level known to be beneficial in the vast majority of patients. The effective initial dosage of *propylthiouracil* has been found to be 300 mg. daily; this amount results in satisfactory response in approximately 95 per cent. of the patients so treated. Larger doses (400 to 600 mg. daily) should be employed in those patients with severe hyperthyroidism and a large goitre. The effective initial dosage of *methylthiouracil* is also 300 mg. daily; again, a larger dose may be necessary in patients with severe disease. With *methimazole* and *carbimazole*, 30 or 40 mg. daily usually suffices.

These drugs are given orally. Their elimination occurs rapidly, and in order to assure an effective concentration in the body the total daily dose is divided into three equal portions for administration at intervals of approximately eight hours. Reliability on the patient's part in taking the drug is essential for, whilst an occasional missed dose apparently does no harm, gross irregularity in taking the medication often results in a poor therapeutic response. It is advisable to outline a dosage schedule to the patient which will facilitate his cooperation: for example, the patient may take the drug at mealtimes or, more preferably, perhaps, on arising, in mid-afternoon and on retiring. The effectiveness of these drugs is so uniform in most patients that when a poor response is observed one is justified in ascertaining if the patient is taking the drug as prescribed.

RATE OF RESPONSE

When the supply of thyroid hormone to the body is discontinued, a progressive decrement in metabolic rate ensues; this develops gradually, however, due to the fact that the circulating hormone, thyroxine, is utilized slowly, an interval of about 55 days being required to exhaust the normal quantity. The hyperthyroid subject deprived of hormone by the action of an antithyroid drug has a slow decrease in metabolic rate, and the period required for the attainment of a normal rate probably depends in large measure upon the amount of circulating hormone at the institution of therapy. Among hyperthyroid patients treated with antithyroid compounds the average interval required to establish a metabolic rate consistent with euthyroidism is 90 days. The approximate extremes are 30 to 180 days. Additional improvement is usually observed with continued therapy, however: further subsidence of nervousness and tension, increase in weight and development of a sense of well-being are achieved during the period extend-

ing well beyond the point of attainment of a normal metabolic rate.

CONCOMITANT ADMINISTRATION OF IODINE SOLUTION

Differences of opinion exist among some clinicians regarding the value of iodine therapy concomitant with antithyroid drug therapy. In my opinion there is no special value in its use with an antithyroid drug in patients with mild or moderately severe thyrotoxicosis, but in patients with severe thyrotoxicosis requiring hospitalization, one may not wish to withhold iodine therapy, as in such instances the known beneficial effects of both agents are indicated. In patients who have received both drugs until a state of near or complete euthyroidism is achieved, it has been noted occasionally that withdrawal of the iodine solution may result in the reappearance of moderate hyperthyroidism, even though the antithyroid drug be continued. Such an occurrence can be corrected either by reinstitution of iodine therapy, or by increasing the dosage of the antithyroid drug for a few weeks.

USE IN PREPARATION FOR SURGERY

Subtotal thyroidectomy for Graves' disease in the days before the development of any type of preoperative medication was a procedure often hazardous to the patient and harrowing to the surgeon. Remarkable improvement in the success of surgical treatment resulted following the introduction of preoperative iodine therapy. Treatment with iodine, however, only ameliorates thyrotoxicosis and in many patients a degree of hyperthyroidism remained which did not eliminate all possible risk to operation.

With the antithyroid drugs a complete restoration to normal metabolic status can be achieved. Thus, the operation can be accomplished with the hazard reduced almost to that attendant upon any subtotal thyroidectomy for non-toxic goitre. It is important to state that thyroidectomy should not be performed until the antithyroid agent has been given for a period sufficient to restore the patient to euthyroidism. Whilst, as already mentioned, this requires about 90 days in most patients, it seems advisable to proceed with antithyroid therapy until *all* the systemic manifestations of thyrotoxicosis are controlled. Thus, the period of preoperative treatment may be five or six months, or even longer in some patients with initial severe disease.

Preoperative administration of iodine solution is indicated in order to achieve involution and decreased vascularity of the gland and should begin two to four weeks before operation. The antithyroid drug should be continued until the day of operation for, if withdrawn one to two weeks before surgery, a degree of hypermetabolism may return within this period which might be deleterious.

The achievement of a secure state of euthyroidism preliminary to subtotal thyroidectomy presents many advantages. The patient enters the surgical theatre with a degree of equanimity not otherwise possible and only with the concern registered by any other person who must undergo an-

æsthesia and surgery. The surgeon, also, approaches the operating table knowing that he may conduct the procedure calmly and without haste, and that he will have adequate time for dissection of the gland, recognition of all-important neck structures and adequate hæmostasis. Anæsthesia is easily induced and maintained. The hazard of postoperative thyroid 'storm' is non-existent, since the patient is not thyrotoxic and since the thyroid gland does not contain an excess of hormone. A time for operation can be selected which is suitable to the patient, the surgeon, and the hospital. In most patients the entire preoperative therapy is conducted on an outpatient basis, and admission to the hospital occurs on the day before operation. Moreover, it appears that the period of convalescence in the hospital is materially shortened by this regimen: the postoperative period of hospitalization rarely exceeds ten days and generally is only five to seven days. Finally, a mortality rate approaching an irreducible minimum appears to have been achieved for thyroidectomy in patients with thyrotoxicosis when the aforementioned principles have been utilized: no operative or postoperative death has occurred at The Johns Hopkins Hospital in the past eight years. At present the greatest recognized value of the antithyroid drugs is their use in the preparation of thyrotoxic patients for surgery.

USE IN PREPARATION FOR RADIO-IODINE THERAPY

Radio-iodine therapy, like subtotal thyroidectomy, is an ablative form of treatment. The removal of the excess thyroid tissue is brought about slowly with radio-iodine; accordingly, the risk of post-treatment thyroid crisis is not great. Nevertheless, in patients with severe thyrotoxicosis or in those with complicating features of a serious degree such as cardiac insufficiency, diabetes mellitus or hypertension, a course of antithyroid drug before treatment with radio-iodine minimizes the likelihood of post-radiation exacerbation of hyperthyroidism. With radio-iodine, as with surgery, the duration of drug therapy before the ablative procedure should be sufficient to produce considerable amelioration of the thyrotoxicosis, although it is hardly necessary to achieve complete euthyroidism as seems wise with surgical treatment.

To some degree the antithyroid drugs prevent accumulation of radio-iodine in the thyroid, although the 'blocking' effect is rapidly lost following discontinuation of the drug. This phenomenon makes it necessary to withhold the antithyroid drug at least two, and preferably four, days before the administration of a therapeutic dose of radio-iodine, in order to ensure an uptake of the radio-isotope which will be adequate to destroy thyroid tissue.

It is well recognized by clinicians who have had experience with radio-iodine therapy that estimation of the dose necessary to effect the desired degree of destruction of thyroid tissue is difficult. The rates of thyroid accumulation and discharge of the isotope, the size of the gland, the distribution of the radio-iodine in the thyroid, and the sensitivity of the thyroid

cells to radiation are factors which must be considered; no methods exist for appraisal of the last two factors. At Johns Hopkins, experience suggests that administration of propylthiouracil before radio-iodine therapy makes even more difficult the assessment of the proper dose of the isotope. In general, it has been necessary to use larger quantities of radio-iodine to achieve dissolution of the 'thiouracilized' gland than is required in patients not previously treated with propylthiouracil. Yet the avoidance of any possibility of exacerbation of thyrotoxicosis with radio-iodine by achieving amelioration of the disease with an antithyroid drug beforehand outweighs, in patients with florid disease, any disadvantage of using a larger total quantity of radiation.

LONG-TERM OR CONTINUOUS USE OF THE ANTITHYROID DRUGS

Following induction of euthyroidism the dosage of the antithyroid drug can be reduced to so-called 'maintenance' levels. This is done in a stepwise manner; for example, the initial daily dose may at first be decreased by one-third or one-half; if euthyroidism persists after several months, the dosage may be reduced again by one-third or one-half. With methylthiouracil, carbimazole and methimazole, which appear to be more potent antithyroid agents than propylthiouracil, the initial dosage can be reduced soon after the attainment of a normal metabolic rate, but with propylthiouracil the initial dosage should be continued for two or three months beyond attainment of normal metabolism before decreasing to maintenance levels, as mild recurrence of hyperthyroidism may develop if the dosage is reduced earlier. Similarly, the development of hypothyroidism during maintenance therapy appears to occur more readily with methylthiouracil, carbimazole or methimazole than with the less potent propylthiouracil. In order to keep the patient euthyroid, minor adjustments of dosage of the former drugs may be more necessary than with the latter.

During the induction of euthyroidism it is advisable to examine the patient at intervals of two weeks. The periods between visits can be extended to one or two months when euthyroidism is attained. Should prolonged therapy exceed one year the interval between each examination can be lengthened to three months. On each visit questions directed towards ascertaining symptoms relating to metabolic status should be asked of the patient, and the examination should include measurement of the degree of exophthalmos with an exophthalmometer, assessment of the extraocular movements, palpation and auscultation of the thyroid gland, determination of pulse rate and blood pressure and such other observations as may be considered pertinent. One should inquire about, and look for, toxic manifestations of the drug. The basal metabolic rate may also be determined at the aforementioned intervals but, as in any other disease, the assessment of the patient's clinical status should hold the greatest influence in guiding therapy.

The antithyroid drugs are goitrogenic agents: when administered to

normal animals they produce hypertrophy and hyperplasia of the thyroid gland. In view of this, it might be anticipated that during their long-term administration to patients with Graves' disease the goitre might increase further in size and, indeed, such does occur in some patients, especially if hypothyroidism results from excess maintenance dosage. Yet, during long-term antithyroid therapy, enlarged thyroid glands not only often decrease in size but may also return to normal. In 81 patients with thyrotoxicosis who received long-term propylthiouracil therapy it was found that the goitre decreased in size in 49 (60.5 per cent.), remained unaltered in 28 (34.5 per cent.) and enlarged in 4 (5 per cent.) (Wing and Asper, 1952), and in one-half of those patients showing decrease in goitre size, the thyroid returned to a size considered normal, as determined by palpation. Whereas those patients with small goitres appear more likely to experience reduction in size of the gland, an occasional patient with a very large goitre may also show slow regression of the thyroid to normal. In some patients the goitre may not alter in size until after many months of therapy.

The exophthalmic component of Graves' disease is little understood, for its occurrence or the degree of its severity when present bears no particular relationship to the severity of hypermetabolism. During long-term antithyroid drug treatment the degree of exophthalmos, as measured with an exophthalmometer, seldom changes significantly, although a few patients may experience remarkable improvement and others, fortunately rarely, marked worsening. There is often an apparent improvement in exophthalmos, not substantiated by actual measurement of the proptosis, due, of course, to the lessened stare, diminution of the width of the lid slits and disappearance of lid-lag which occur commensurate with the attainment of euthyroidism. Exophthalmos appears less likely to worsen with long-term antithyroid drug therapy than following the ablative types of therapy, although statistical confirmation of this is lacking at present.

What constitutes a long-term course of antithyroid drug therapy? To this question at the moment there is no satisfactory answer. The aim of such treatment is to achieve permanent correction of the disease, but the duration of treatment necessary to accomplish this, if indeed it can be accomplished in all patients, is not known. In general, most clinicians have administered the drug for about one year. Markedly divergent incidences of remission of the disease following long-term therapy have been reported by various authors, but in an extensive compilation of the published reports from many clinics Solomon and his associates (1954) report an average remission rate of 54 per cent. in those patients who had received a single course of antithyroid medication and who had been followed for one year or more after cessation of treatment.

Some of the factors which are of importance in the success or failure of long-term therapy have also been delineated by Solomon and his colleagues. Of unique importance in predicting the likelihood of long-lasting remission is decrease in goitre size for, of those patients whose goitres diminished in

size during therapy, the remission rate (67 per cent.) after treatment was more than twice that (31 per cent.) of patients whose goitres remained unchanged or increased in size during therapy. Age, sex, type of goitre, severity of hyperthyroidism, previous iodine treatment, recurrence after subtotal thyroidectomy or type of antithyroid drug administered do not influence the outcome of antithyroid therapy. Assessment of the value of protracted or even continuous therapy in those patients whose hyperthyroidism rapidly reappears following decrease or discontinuance of maintenance dosage is now being investigated. In our clinic a few patients have received propylthiouracil for five years with control of the disease and without ill-effect.

Poate (1950) and Fraser and Wilkinson (1953) have recently considered the advisability of administering desiccated thyroid or thyroxine in addition to the antithyroid drug as soon as the patient attains normal metabolic levels. The obvious advantage of this is that myxœdema resulting from inadvertent overdosage of antithyroid drug during prolonged maintenance therapy cannot occur. Theoretically, this therapy holds another advantage: since thyroid hormone administered to a normal subject results in a decrease in size of the thyroid, with so-called 'atrophy of disuse', it may well be that the hyperthyroid patient whose disease is controlled with an antithyroid drug might also show a decrease in the size of the thyroid with added thyroid hormone and thus more likely experience a long-lasting remission after therapy.

TOXIC REACTIONS

The toxic or hypersensitivity reactions to the antithyroid drugs are few, but unfortunately, when they occur, interruption or discontinuance of this form of treatment is usually necessary. Thiouracil has the greatest toxic propensities and produces *agranulocytosis* in such frequency that it should be used only with the greatest caution and care. Indeed, in the United States, the Council on Pharmacy and Chemistry of the American Medical Association does not sanction its clinical use. Methyl- and propyl-thiouracil, carbimazole and methimazole may also produce agranulocytosis, but with far less frequency than thiouracil. No method now exists to determine which patients may show this reaction to the drug; moreover it may develop at any time during treatment. In one patient in our series agranulocytosis appeared after eight months of propylthiouracil therapy. The symptoms heralding the appearance of agranulocytosis are usually sore throat and fever. The onset may be rapid and on occasion has been noted two days after a previous count of the white blood cells was within normal range. On the other hand, agranulocytosis may develop slowly over a period of a few days or weeks, the number of granulocytes slowly decreasing in the peripheral blood.

Whilst agranulocytosis is to be respected, it should not be feared. The duration of agranulocytosis, when it occurs, is usually limited to approximately five days following withdrawal of the offending agent, after which

there is a generous outpouring of juvenile granulocytes into the peripheral blood. Counter-measures include cessation of antithyroid drug administration and protection of the patient against fulminating infection by the use of penicillin or other appropriate antibiotics. Moreover, although extensive experience is lacking, adrenocorticotrophic hormone (ACTH) or cortisone appears to be most valuable. In one of our patients with agranulocytosis, cortisone, 100 mg. initially followed by 50 mg. every four hours thereafter, was started eighteen hours after cessation of propylthiouracil therapy. Within four hours the differential count of juvenile granulocytes had risen from zero to 58 per cent., and within twenty-four hours the total and differential counts of the white blood cells were entirely normal. Cortisone dosage was rapidly reduced and discontinued on the third day.

Leucopenia may also appear during treatment with antithyroid drugs. It should be recalled, however, that leucopenia is not uncommon in patients with untreated thyrotoxicosis; therefore its appearance during therapy need only call for increased frequency in executing repeat counts. Should the count of the white blood cells be less than 4000 cells per c.mm. a differential count is necessary. In the presence of marked granulopenia (i.e., less than 25 per cent. granulocytes) cessation of antithyroid therapy is indicated. If there is only a slight reduction in the number of granulocytes, however, the drug may be continued provided the patient and the total and differential counts of the white blood cells are observed closely; if the defect persists such patients should receive ablative rather than long-term drug therapy.

Urticaria may also occasionally complicate drug therapy. Its initial appearance is usually about fourteen days after beginning treatment. Subsidence occurs slowly following withdrawal of the drug, but the symptoms may be alleviated more rapidly with antihistaminic agents or, if severe, with cortisone or ACTH. If the antithyroid drug is again administered the hives rapidly develop, usually within three days. Urticaria necessitates cessation of therapy, for it does not seem practicable to attempt to give antihistaminic drugs, cortisone or ACTH for the long period required to bring the thyrotoxicosis under control with the antithyroid drug. It is possible, however, that substitution of another antithyroid drug may not be met with the same reaction. Herein lies one of the values of methimazole and carbimazole, for their chemical configuration is sufficiently different from the thiouracils to warrant their trial in such instances; the converse holds for propyl- or methyl-thiouracil if methimazole or carbimazole should produce urticaria.

Many other toxic reactions to antithyroid drugs have been noted, but occur rarely. The skin may be affected by *pruritus*, *alopecia*, or *erythema bullosa; thrombocytopenic purpura*, *lupus erythematosus-like manifestations*, and *polyarteritis nodosa* have also been reported.

EFFECT ON PERSONALITY STATE

It is often noted that occasional patients with Graves' disease may retain some symptoms suggestive of hyperthyroidism following successful subtotal

thyroidectomy. Such symptoms, especially nervousness, are often similar to those which existed when hyperthyroidism first appeared although recurrence of the disease is not established by examination of the patient. This phenomenon is also occasionally observed following radio-iodine therapy. However, most patients receiving long-term antithyroid treatment show a remarkable change in their nervous response to stressful stimuli. Slowly they achieve a normal pattern of daily living, and the nervous manifestations of hyperthyroidism recede. Following discontinuance of therapy, the reappearance of such symptoms usually heralds the approach of a recurrence of hyperthyroidism. Moreover, our limited experience suggests that if during long-term drug therapy such symptoms do not regress, prompt recurrence of hyperthyroidism usually follows cessation of treatment. On the other hand, those patients who experience a persistent remission after long-term therapy do not have such symptoms, which, as aforementioned, are occasionally seen in patients who receive ablative therapy.

CONCLUSION

Successful clinical application of a number of chemical agents which prevent thyroidal synthesis of thyroid hormone has inaugurated a new era in the management of hyperthyroidism. These compounds, chiefly propylthiouracil, methylthiouracil, methimazole and carbimazole, are known as 'antithyroid' drugs, and upon administration in proper dosage each will alleviate the hypermetabolic features of hyperthyroidism.

The antithyroid drugs have received widespread use in the preparation of thyrotoxic patients for subtotal thyroidectomy. Remarkable improvement in the morbidity and mortality of this operative procedure has thus been achieved. These drugs likewise may be employed to prepare severely thyrotoxic patients for radio-iodine therapy.

The beneficial effects of these drugs in the long-term treatment of hyperthyroidism have been amply demonstrated. Approximately one-half of the patients receiving such therapy experience a prolonged remission of hyperthyroidism following cessation of treatment. The well-recognized efficacy of the antithyroid drugs, along with moderate cost, simplicity of administration and low incidence of toxic reactions, affords these compounds a secure position in the therapeutic armamentarium of hyperthyroidism.

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REVISION CORNER

THE TREATMENT OF ACNE VULGARIS

At puberty the sebaceous glands undergo hypertrophy, probably as a result of stimulation by androgens. In acne this process is exaggerated and there is an accumulation of sebum within the enlarged glands and their ducts, and a hyperkeratosis of the mouths of the pilosebaceous follicles. This sebum acts as a foreign body, producing an inflammatory reaction with the formation of pustules, cysts and subsequent scarring. Bacteria serve only as secondary invaders. These changes may be brought about by an increase in the androgen/œstrogen ratio or, in the case of females, in the androgen and progesterone/œstrogen ratio; but despite much recent research, hormone therapy alone is of little value. The best results are obtained if treatment is directed against the local abnormalities in the skin and the various factors that are found to aggravate the condition in each individual patient. Undue emphasis on one aspect of the problem will lead to disappointing therapeutic results.

The ultimate aim of acne therapy is to prevent scarring, and early treatment is of prime importance.

LOCAL TREATMENT

This is designed to remove excessive sebum and to produce a mild peeling effect in order to empty the follicles. Frequent washing is the first essential, and should be carried out four or five times daily. Sulphur is the most useful peeling agent and may be applied in the form of a lotion:—

Sulphurated potash	80 grains (5.2 g.)
Zinc sulphate.....	80 grains (5.2 g.)
Water .....to	8 fluid ounces (227 ml.)

This lotion is allowed to dry on the skin and the residual powder is rubbed in.

Another preparation with a penetrating base is the following, which is well tolerated by fair-skinned patients:—

Sulphurated potash	10 grains	(0.6 g.)
Zinc sulphate.....	10 grains	(0.6 g.)
Propylene glycol	60 minims	(4 ml.)
Emulsifying wax	15 grains	(1 g.)
Carbowax 1500	90 grains	(6 g.)
Water .....to	1 fluid ounce	(28.5 ml.)

Some patients do better with a cream than a lotion, for example:—

Precipitated sulphur	15 grains	(1 g.)
Salicylic acid	10 grains	(0.6 g.)
Propylene glycol	30 minims	(2 ml.)
Emulsifying wax	40 grains	(2.6 g.)
Soft yellow paraffin	40 grains	(2.6 g.)
Carbowax 4000.....	240 grains	(16 g.)
Water .....to	1 fluid ounce	(28.5 ml.)

Acne affecting the forehead and hair margin may resist treatment if the associated seborrhœa of the scalp is neglected, and the above cream may be applied once or twice a week according to individual tolerance. It has the added advantage of being easily removed. If comedones persist despite the use of peeling agents, they are gently removed with a comedone expressor. These instruments should have a

hole which will just admit a normal-sized pin. If a larger hole is used, the attempts at removal will lead to further injury and scarring. For the same reason squeezing of pustules with the fingers must be discouraged.

There is much individual variation in reaction to peeling agents, and fair-skinned patients should be warned to stop treatment if the skin becomes irritable. The aim of treatment is to produce a scarcely visible peeling which is sufficient to remove the majority of comedones and open papules and pustules. If the face becomes sore, a cream should not be used; the inflammation is allowed to subside or, if unusually severe, wet dressings may be applied. Many patients gradually develop a tolerance for these remedies and it may be necessary to increase the strength or the number of applications to maintain their effectiveness. All cosmetic creams and oily hair dressings are prohibited, but the occasional use of face powder does no harm.

Ultra-violet light is particularly useful for pustular acne of the back and chest, but it stimulates keratinization and must be followed by vigorous local treatment with sulphur applications.

Carbon dioxide snow in the form of a slush with acetone is probably the most effective peeling agent for deep pustular and cystic acne with scarring, and may be applied at intervals of one or two weeks. The slush is placed on a wooden spatula covered with gauze. A temporary whitening of the skin occurs as the spatula is firmly painted over the affected areas, and erythema and scaling occur after an interval of a few days. The number of applications is best adjusted to the individual and, to avoid undue soreness, it is advisable to withhold sulphur applications for a few days after each application.

GENERAL TREATMENT

Diet.—Certain foods aggravate acne, but there is much individual variation and this may be determined by the history. As a general rule, excess of fats and sweets is avoided, and a reducing diet in the obese patient is often followed by improvement. Chocolate in any form, nuts and fat derived from the pig are particularly liable to produce exacerbations.

Acneform eruptions may follow the administration of medicines containing iodides and bromides and they are best avoided in these patients. For the same reason, seborrhœic individuals should not be employed in occupations involving contact with oil or with chlorinated naphthalenes.

Fatigue has an adverse effect on acne. For example, school children who are working for examinations may fail to respond to treatment because of inadequate sleep.

Environment.—An unsatisfactory home environment has a similar effect and the cooperation of parents is necessary in order to encourage patients to lead a normal social life and to prevent them from becoming self-conscious about their appearance.

These measures will control the majority of mild cases of acne vulgaris, but there are some patients with deep nodular and cystic acne in whom routine treatment fails, and the following additional remedies may be considered.

Hormone therapy is useful in patients who develop acne after adolescence or in those women who experience marked exacerbations just before or during menstruation. Diethylstilbœstrol in a dose of 0.5 mg. daily is given seven days after the completion of the menses until the onset of the next period. It is im-

portant to use this interval in order to avoid upsetting ovulation and the menstrual cycle. Treatment is discontinued if no response occurs after three to four months. There is considerable difference of opinion concerning the value of hormone therapy in males. Small doses of œstrogens are well tolerated, but treatment should be restricted to deep-seated eruptions persisting after adolescence.

X-ray therapy is justified in patients who fail to respond to the measures described and will often reduce the excessive secretion of sebum. A dose of 100r is repeated four or five times at weekly intervals. A second course may only be given after an interval of at least six months, and a total dose of 1500r should not be exceeded because of the danger of producing a radiodermatitis. Local treatment with peeling agents must of course be continued after treatment.

Antibiotics are of little value in this disease because bacteria merely act as secondary invaders. In cases in which there is much secondary infection, temporary benefit occurs with systemic treatment but a relapse usually follows when it is discontinued. An additional reason for avoiding the use of local antibiotics is the danger of producing a sensitization eczema.

It has been suggested that acne may persist after puberty because of an arrest of emotional and psychosexual development at the adolescent stage. Alternatively, this retardation could be due to the emotional damage produced by a disfiguring disease at the time of life when the personal appearance is of most importance. It is for this reason that early and prolonged treatment of the mildest case is of the utmost importance.

ERIC WADDINGTON, M.D., M.R.C.P.
Consultant Dermatologist, United Cardiff Hospitals, and Welsh Regional Hospital Board.

THRUSH

THRUSH (moniliasis) is caused by a fungus, *Monilia albicans* (*Oidium albicans*). This is normally a saprophytic inhabitant of the mouth but it may become pathogenic if local tissue resistance is lowered. Premature or feeble infants, undernourished children and old people are especially susceptible to infection. In the neonatal period healthy infants may be infected. Infection may be spread by means of teats, bottles, and the hands of mothers and nurses contaminated by the spores of monilia. Thrush may easily be spread in a nursery unless proper precautions are taken. Ludlam and Henderson (1942) found the fungus present in 11 out of 60 babies in a nursery for new-born babies, eight of whom developed clinical thrush by the age of ten days.

Maternal moniliasis is probably the principal source of infection in new-born babies. Monilia is often present in the vaginal secretions of pregnant women, and there is a positive correlation between maternal vaginal and infantile oral moniliasis.

ORAL MONILIASIS

Clinical appearance.—In oral moniliasis the lesions are characteristic. They are seen on the gums, buccal mucosa, sides of the tongue and the throat. The lesions may be few and scattered, or many and almost confluent. Typically, a milky-white patch is visible which, if removed, leaves a red abraded area of mucous

membrane. This distinguishes the lesions from milk curds which can be easily wiped away. There is no pain and, if the infection is limited to the mouth, no constitutional symptoms. Enlargement of the cervical lymphatic glands does not occur. Healing takes place after a few days' treatment.

The diagnosis may be confirmed by teasing out a fragment of a lesion on a slide to which a drop of 10 per cent. potassium hydroxide has been added. The jointed filaments and spores can then easily be seen. The fungus may be cultured on Loeffler's medium, when the large spores can be easily recognized.

TREATMENT

Attention must be directed to the general nutrition of the infant and to his feeding. Disappearance of the thrush is often due to the improvement of nutrition rather than to any local treatment. In healthy new-born infants the disease is probably self-limited and will clear up spontaneously. The application of mild antiseptics, however, appears to hasten recovery. Glycerin and borax is a time-honoured remedy. A 0.5 per cent. aqueous solution of gentian violet is now commonly used. The lesions are painted with a wooden or metal applicator, the end of which is covered with cotton-wool and dipped in the solution. Applications should be given twice or thrice daily at first; when the lesions are healing, once daily should be sufficient.

Recently a new preparation, stilbamidine, has been introduced for the treatment of moniliasis. Its disadvantages are that it is expensive and has to be made freshly every forty-eight hours. It is made up in a 0.5 per cent. solution.

OTHER SITES OF MONILIAL INFECTION

Monilia infections may occur in other situations than in the mouth.

The skin.—Infections may occur at the angles of the mouth (perlèche). There may be a generalized papulo-vesicular scaling lesion of the skin, or localized lesions may occur around the anus and genitals, or between the fingers. Diagnosis rests on the discovery of the monilia in the lesions.

Local applications of 1 per cent. iodine or an ointment containing 1 per cent. salicylic acid and 2 per cent. precipitated sulphur are useful in the treatment of monilia of the skin.

The gastro-intestinal tract.—Thrush œsophagitis rarely occurs in the normal healthy infant. It is met with in premature babies, infants with very poor nutrition, or those suffering from severe debilitating infections. It may occur from spread of infection from the mouth or it may be a primary lesion. The appearances are the same as those in the mouth. Unlike thrush lesions in the mouth those in the œsophagus give rise to pain and the infant screams immediately after feeds, which are often refused. Regurgitation of food is frequent. Blood streaks may be seen in the vomit. The constitutional symptoms may be severe and the infant may show all the signs of generalized toxæmia. This may cause the infant's death or he may die of secondary broncho-pneumonia. The prognosis in severe œsophageal thrush is always serious. Ebbs (1938) reported a series of 22 fatal cases. The thrush lesions in the œsophagus are inaccessible to treatment but the administration of alkalis, such as aluminium hydroxide, gives some relief.

Thrush in the stomach, ileum and colon has been described, usually associated with very severe constitutional symptoms. Monilia can often be identified in the stools of such cases.

Thrush pneumonia.—Monilia infection of the lungs may occasionally occur, due to aspiration of spores from mouth lesions. Adams (1944) has reported seven cases of pneumonia in infants with oral thrush. The presence of pneumonia was confirmed by x-ray examination. In the one infant who died, a widespread staphylococcal pneumonia with multiple abscesses was found. He suggested that *M. albicans* and a strain of staphylococci have a synergistic action in the causation of the pneumonia.

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GEORGE NEWNS, M.D., F.R.C.P.
Physician, The Hospital for Sick Children, Great Ormond Street.

NOTES AND QUERIES

Sensitizing Agents in Cosmetics

QUERY.—Some of my patients show a positive reaction to patch tests of a combination of all of the following chemicals, which are used in a certain cosmetic for the face. I am not in a position to carry out further individual chemical and skin tests and would be grateful if you could tell me which might be the offending agent(s), either separately or in combination, at the first or at subsequent applications:—

Propylene glycol
Lecithin (from soya bean)
Propylene glycol monostearate
Polyoxyethylene sorbitan monolaurate
Sorbitan monolaurate
Propylene glycol monolaurate
Talc
Kaolin
Betonite
Titanium dioxide
Triethanolamine
Stearic acid, triple pressed
Woolwax alcohols
White oils
Iron oxide pigments
Methyl ester of parahydroxybenzoic acid
Propyl ester of parahydroxybenzoic acid
Lanolin

REPLY.—It is impossible to say which could be the offending agent(s) in this list without patch tests with the separate constituents of the cosmetics concerned. The powder constituents, such as talc, kaolin, betonite and titanium dioxide, are unlikely, but any of the others might cause a reaction if the individual is sensitive. Perfume or the emulsifying chemicals are common sensitizing agents in cosmetics; sun exposure may also precipitate dermatitis in patients photosensitized by perfumed cosmetics. It might be wise to ask the cosmetic firm in question for advice; the majority are most helpful and will often supply patch-test materials. Alternatively, certain firms make non-allergic cosmetics which can usually be employed by patients showing cosmetic sensitivity: e.g., Bencard's non-allergic cosmetics and Queens cosmetics.

GEOFFREY HODGSON, M.B.E., D.M.

Treatment of Overactive Pilo-Sebaceous Glands

QUERY.—A thirty-year-old male patient has enlarged pilo-sebaceous openings on his forehead, nose and malar regions. Regular washing with soap and water, and the application of astringent lotions have not brought about any improvement. He has a mild seborrhœa of the scalp, which is controlled by regular shampooing.

I would be grateful for any advice which you could give me in dealing with this case.

REPLY.—Activity of the pilo-sebaceous glands is largely dependent upon racial and familial characteristics and more directly on androgen and progesterone activity. Treatment of young males with œstrogen, however, is not satisfactory as the dosage necessary to influence sebaceous activity will produce undesirable side-effects.

Treatment should aim at correcting any contributory factor which may be present. Excess of fat and carbohydrate in the diet should be avoided. Any tendency to rosacea, shown by a liability to flush easily and by telangiectasia of the skin of the forehead, cheeks and chin should be corrected. In this type of case a lotion containing sulphur, 1% to 2%, applied at night, with sedation and avoidance of hot or spiced foods may cause improvement. Flatulence and

indigestion should be investigated and treated. Superficial x-ray therapy will depress sebaceous activity, at least for a time. It should be repeated only with caution.

Patients with Parkinsonism, advanced cerebral tumours, schizophrenia and adrenal tumours may develop excessively greasy skins, and it should be remembered that complaints of enlarged pores made by otherwise healthy young patients may be the product of an early paranoid or schizophrenic psychosis.

R. G. HOWELL, M.B., CH.B.

Diabetic Retinitis

QUERY.—A patient who has for several years suffered from chronic diabetes was recently operated on for senile enlargement of the prostate and is now convalescing. He has advanced diabetic retinitis, together with sensory ataxia of both lower limbs, of a severe type. He has had requisite treatment with insulin, B complex, liver extract, B_{12}, and so on, but there has been no satisfactory improvement in the neuritic condition. Kindly let me know the prognosis of the retinitis, and treatment if any. Also, please inform me of any other therapy which may reduce the ataxia.

REPLY.—It is difficult to give the prognosis in a case of diabetic retinitis without details of the fundus changes, but, if there is no evidence of retinitis proliferans, it is usually true to say that the patient will not go blind, although he may lose visual acuity to a considerable degree and may be unable to read any but the largest print. The majority of these cases, however, are able to get about without assistance.

With regard to what I imagine is a severe neuropathy or myelopathy, there is no known satisfactory treatment for this condition, but large doses of vitamin B_{12} with the possible addition of testosterone are worth a prolonged trial.

WILFRID OAKLEY, M.D., F.R.C.P.

Tetanus Prophylaxis

QUERY (from a reader in South Africa).—I should be grateful for advice on the following points:—

(1) Should one give antitetanus serum in general practice in the case of every wound or only in those which might be soil contaminated? For example, would one give it to someone who has a needle prick in the finger, or who cuts himself at home? Here the chances of contamination with soil, the nidus of the organism, are minimal.

(2) If antitetanus serum is given (e.g., 1,500 I.U.) how long after the occurrence of the wound is it effective—for example, supposing a man injured himself four or five days before being given the prophylactic dose of serum, would it have any effect?

(3) If a man has an injection of 1,500 I.U. of A.T.S. and then injures himself again, say six weeks later, should he be given a further dose? In other words, how long does the protective effect of the serum last?

(4) Finally, how does one give the serum in a person who has a history of asthma? Is it necessary to take special precautions in every case or only when there is a history of allergy?

REPLY.—(1) Prophylactic antitoxin for passive immunization should only be given after wounds in which there is a reasonable possibility of tetanus infection. A needle prick in the finger is very unlikely to cause tetanus if it is kept clean but if it becomes infected and leads, for example, to a whitlow, it may do so. A clean cut sustained in the home is unlikely to cause it provided it is kept clean, but every case must finally be judged on its merits.

(2) The effectiveness of a dose of prophylactic antitoxin depends upon many factors, but particularly upon the rate at which toxin is produced in the wound and absorbed into the circulation. If the wound is heavily infected, antitoxin must be given within a few hours, for protection. If the wound is slight, an injection given much later may be effective. It should also be remembered that tetanus infection does not necessarily occur at the time the wound is inflicted but may gain access later. The effect of a single dose of antitoxin becomes rapidly less during the week following injection, but some activity may last for two or three weeks.

(3) A further injection of antitoxin should certainly be given even after an interval of one week. In this connexion a recent paper by Littlewood, Mant and Payling Wright (*Brit. med. J.*, 1954, **ii**, 444) is worth noting. In this they describe a case in which they attribute failure to protect to a state of hypersensitivity to the foreign serum proteins which had been induced by a similar prophylactic injection six months before. They recommend that once a person has received an injection of any horse serum antitoxin he should be promptly immunized against diphtheria and tetanus with the appropriate toxoid.

(4) If a person gives an allergic history, or it is suspected that he may be sensitive to horse serum, special precautions should be taken. A mild dose, say 0.025 ml., may first be given subcutaneously, the dose being doubled every fifteen minutes until the required amount has been given. A solution of adrenaline, 1:1000, should also be available, to give subcutaneously in case of reaction. It is not usually considered

necessary to take special precautions in every case.

Finally, it cannot be too strongly emphasized that active immunization is the prophylactic method of choice in preventing tetanus.

LESLIE B. COLE, M.D., F.R.C.P.

Diet in Gout

QUERY.—I have a patient who is suffering from mild gout in a subchronic form. Could you please give me a comprehensive list of individual foods, wines, beers, with the purin percentage content appended?

REPLY.—The purin content of some of the common foods is shown in the following table:—

Material (all cooked)	Purin nitrogen per 100 g. edible food
Brains	0.033
Mutton (general average)	0.063
Fish " "	0.065
Pork " "	0.069
Beef " "	0.081
Birds " "	0.094
Hearts	0.116
Cod roe (hard)	0.120
Liver and kidneys	0.140
Herring (no roes)	0.150
Smelts	0.168
Sprats	0.180
Sardines	0.234
Whitebait	0.327
Throatbreads, sweetbreads, etc.	0.426
Herring roe (soft)	0.480
Oxo cubes	0.236
Bovril	0.324
Marmite	0.356

It will be seen that all these foods contain some purins. Some of them, like herring roes (soft), throatbreads, sweetbreads, whitebait and sardines, should never be taken as they contain large amounts. Those foods which contain less than 0.116 g. of purin nitrogen per 100 g. (3½ ounces) can be eaten in ordinary amounts. The foods which contain 0.116 to 0.180 g. of purin nitrogen may be eaten, provided that the amounts taken are smaller. Thus, 1¾ ounces of cod's roe (hard) or 1¼ ounces of sprats, can be eaten instead of 3½ ounces of white fish, without increasing the amount of purins eaten. Oxo, Bovril and Marmite all contain large amounts per 100 g. and should not be taken as an addition to the diet. They may be taken in small amounts, e.g., ½ to 1 ounce, if other foods cannot be eaten for any cause.

Tea, coffee and cocoa contain so little that they can be taken in ordinary amounts. Wines and beers do not contain purins but it is believed that beer and stout, red wines and champagne should not be drunk as they may precipitate an attack. Cider, white wines and sherry do not upset most people; a few people are said to be upset by white wines and not by red wines.

GEORGE GRAHAM, M.D., F.R.C.P.

Autohæmotherapy

QUERY (from a reader in Pakistan).—What are the indications for autohæmotherapy? On what principle does it act? Some doctors prescribe it for the treatment of microcytic hypochromic anæmia. Can autohæmotherapy cure anæmia?

REPLY.—There are no definite indications for the employment of autohæmotherapy. It is used as a non-specific immunizing or desensitizing technique in the same way as injections of peptone might be given. It has been advocated mostly in the treatment of vasomotor neuroses, asthma and various dermatological conditions. When efficacious, its mode of action is not clear, although one report has put forward the view that autohæmotherapy may cause adrenocortical stimulation; a fall in circulating eosinophils was noted after the intramuscular injection of 10 ml. autogenous blood, but no such change occurred when saline was used as a control. Some dermatologists have employed autogenous human serum for re-injection intravenously, but in view of the risk of serum jaundice, it is most important to remember that this should be the patient's *own* serum. For the same reason and for the additional danger of immunization by heterologous blood group antigens, whole blood other than that of the patient should never be injected intramuscularly.

There are no grounds for believing autohæmotherapy to be of value in the treatment of microcytic hypochromic anæmia.

J. N. MARSHALL CHALMERS, M.D., M.R.C.P.

PRACTICAL NOTES

Treatment of Ankylosing Spondylitis

IN a survey of the present status of ankylosing spondylitis, F. Dudley Hart (*Annals of the Rheumatic Diseases*, September 1954, **13**, 186) states that 'the therapeutic pendulum has today swung away from emphasis on rest and fusion in a good position to a programme of much greater activity'. Supporting jackets have been replaced by exercises and postural drill. 'Various forms of physiotherapy may occasionally give symptomatic ease, but they may on occasion aggravate symptoms'. Manipulation 'has little or no part to play in therapy'. Phenylbutazone is a 'useful drug' in both the early acute stage and later: 'indeed, it is one of the most useful drugs for the fused spondylitic, who, with

advanced crippling disease, still experiences much pain', but toxic side-effects must be carefully looked out for. Cortisone and ACTH are useful in the acutely painful exacerbations, whilst the former is also 'of use in the prolonged suppressive treatment of the occasional patient who continues to deteriorate on other therapeutic measures'. Deep x-ray therapy 'gives more lasting results than any other'. Surgery 'has a very restricted part to play in this disease'.

Izoniazid in Miliary Tuberculosis in Children

DETAILS are given by W. P. Sweetman and E. F. Murphy (*Archives of Disease in Childhood*, August 1954, **29,** 338) of the results obtained in four children with miliary tuberculosis treated with isoniazid: 10 mg. per kg. of expected body weight daily. Treatment was continued for a year and all recovered, even though one case was complicated by tuberculous meningitis and one by tuberculous enteritis. In all four cases, clinical improvement began within a few days of starting treatment. Radiological clearing of the lung fields was slower and did not become obvious for six to twelve weeks, but all had a normal radiological appearance after a year. No toxic effects were observed. The authors conclude: 'The treatment of miliary tuberculosis, in children especially, by a long course of injections is unpleasant for all concerned. Izoniazid (in the form of syrup) is in contrast readily taken by children. This ease of administration probably more than compensates for the risk of drug resistance which, in the case of miliary tuberculosis, is, at present, largely theoretical'.

Hydrocortisone Ointment in Dermatology

IN a series of 71 cases of 'superficial inflammatory dermatitis, mostly chronic eczematous dermatitis and atopic dermatitis' treated with hydrocortisone ointment, F. D. Malkinson and G. C. Wells (*British Journal of Dermatology*, August-September 1954, **66,** 300) found that 'in nearly two-thirds of cases hydrocortisone had a positive effect as compared with the ointment base. Of these a quarter responded better to hydrocortisone than to any other topical therapy'. The ointment consisted of 2.5% hydrocortisone acetate in a base of liquid paraffin, petrolatum, cholesterol and multiwax, applied very thinly to affected areas of the skin thrice daily. The eleven cases in the series which responded better to hydrocortisone than any other form of treatment consisted of: three cases of chronic neurodermatitis in adults (out of 17 cases treated), one case of seborrhœic dermatitis (out of nine cases treated), three cases of pruritus ani (out of five cases treated), four cases of chronic itching otitis externa (out of seven cases treated). 'Entirely negative results were seen' in generalized dermatitis, psoriasis vulgaris, pemphigus vulgaris, and in chronic discoid lupus erythematosus. Treatment was discontinued in four cases on account of the irritation it caused. Chronic cases usually relapsed on cessation of treatment.

'Antrenyl' in Emphysema

'SIGNIFICANT therapeutic benefit was observed' in 38 out of 45 patients with emphysema and bronchospasm, following the administration by aerosol of 'antrenyl' (oxyphenonium bromide), a new anticholinergic drug, according to A. Leslie *et al.* (*Diseases of the Chest*, September 1954, **26,** 295). The dosage was 0.5 mg. diluted to 1 ml. with distilled water. This was placed in a nebulizer mounted on an oxygen tank and delivered at a pressure of 20 cm. of water. 'It was thus administered as a nebulized aerosol over the course of 20 minutes of intermittent positive pressure breathing'. It is reported that 'no significant drying effect of this drug was observed in this group of patients, all of whom had copious bronchial secretion'. As it is an anticholinergic preparation, however, such depression of secretion is to be expected. 'For this reason this drug presumably should not be used in the treatment of bronchial asthma, but should be reserved for conditions in which some diminution of the bronchial secretions would not be harmful. Therefore it should be useful in the treatment of bronchospastic conditions associated with the production of considerable sputum'.

Hæmatemesis in the Elderly

A SERIES of 116 patients over 60 years of age, who were admitted to the Royal Infirmary, Edinburgh, during the eight-year period, 1944-51, on account of frank gastro-duodenal hæmorrhage has been analysed by A. W. Branwood and R. F. Robertson (*Edinburgh Medical Journal*, September 1954, **61,** 305). The large majority of the patients (84, or 72%) had a chronic peptic ulcer, and there were only four cases of carcinoma of the stomach. There were no cases of portal hypertension. In referring to the high incidence of chronic peptic ulcer the authors comment: 'This fact is of considerable importance to the surgeon who need not greatly fear finding a cause other than chronic peptic ulcer, when operation is otherwise indicated, even in the absence of a definite initial diagnosis'. Of

the 116 cases in the series, only eight were treated surgically. The over-all mortality for the group was 19%, and this occurred among the patients with chronic peptic ulcer. Of the 24 patients with chronic gastric ulcer, 11 (46%) died, and there were four deaths (8.3%) among the 61 patients with chronic duodenal ulcer. These deaths all occurred in patients with recurrent hæmorrhage, and the incidence of such recurrent hæmorrhage was much higher among those with gastric ulcer (12 out of 24 cases) than among those with duodenal ulcer (12 out of 60 cases). Thus, of the 12 cases of chronic gastric ulcer with recurrent bleeding, only one patient survived, and 'he owed his life to a timely emergency gastrectomy'. There were no deaths among the 86 cases without recurrence of bleeding: in all of these the treatment was 'purely medical'. Of the eight cases with recurrent bleeding treated surgically, six recovered. The authors conclude: 'Irrespective of initial diagnosis of the cause of bleeding, which is often difficult to make, the prognosis is excellent with conservative medical treatment, provided that the hæmorrhage does not recur. Recurrence of hæmorrhage not only indicates the probability of a chronic peptic ulcer but also constitutes a grave emergency with a distressingly high mortality rate in the absence of surgical treatment. If the patient is known to have a chronic gastric ulcer recurrence of hæmorrhage makes surgical treatment imperative'.

Chlorpromazine in Labour

CHLORPROMAZINE 'possesses distinct merit as an addition to the agents employed in the management of labour' in the opinion of B. B. Hershenson *et al.* (*New England Journal of Medicine*, August 5, 1954, **251**, 216), based upon their experience in using it in 100 confinements. Their 'recommended regimen of medication during labour' consists of 'a barbiturate as a psychic sedative, scopolamine as an amnesic agent and chlorpromazine as a psychomotor antagonist'. Chlorpromazine was always given intramuscularly as a 2.5% aqueous solution (*p*H approximately 4.9). The 'regimen' consisted of 'seconal', 180 mg. orally or rectally early in established labour. When the patient first complained of pain (usually ½ to 1 hour after the 'seconal') she was given 25 mg. of chlorpromazine and 0.4 mg. of scopolamine intramuscularly. This combination was repeated two hours later and every two hours thereafter. In patients with 'increased psychomotor activity', an additional dose of chlorpromazine, 12.5 mg. intramuscularly, was given as required. The total dose of chlorpromazine in any one case was limited to approximately 100 mg. Cardiovascular, respiratory, hepatic, renal or metabolic complications were looked upon as contraindications to the use of chlorpromazine. The anæsthetic used for delivery was 'an inhalational procedure in most cases, nitrous oxide, oxygen and ether being used in sequence. . . . When the patient had been adequately medicated to the recommended amount little inhalation anæsthesia was required'. The majority of women had satisfactory amnesia analgesia after the second injection of scopolamine and chlorpromazine, and no ill-effects were encountered in the babies.

Erysipeloid in Fish Workers

A SERIES of 235 cases of erysipeloid of Rosenbach seen in the Aberdeen Royal Infirmary between June 1952 and December 1953 has been reported by D. M. Proctor and I. M. Richardson (*British Journal of Industrial Medicine*, July 1954, **11**, 175). There was a marked seasonal incidence, 217 of the cases occurring in the four-month period, June to September. Practically all the cases (96%) occurred among fish workers; four of the patients were butchers. There was a definite history of trauma preceding the infection in 178 cases. The incubation period ranged from one to over fifteen days, but in 106 of the 160 cases in which it could be calculated, it was less than four days. Pronounced general symptoms did not occur. Lymphangitis, and/or axillary lymphadenitis, was noted in 39 cases (16%). The local skin lesion is characteristic: a pink blush which spreads and becomes violaceous, being accompanied by stiffness of adjoining joints. There is no pus, except in the presence of secondary infection. The average duration of attendance at hospital for this series was seven days (range of two to twenty-seven days). Treatment consists of intramuscular penicillin, and 10% ichthyol in glycerin locally. The precise mode of infection is still in doubt. Preliminary bacteriological investigation showed that *Erysipelothrix rhusiopathiæ*, the causative organism, could not be isolated from sea-fresh fish landed and preserved under aseptic conditions, but that it was isolated 'with ease' from fish in the market.

Prevention of Post-Radiation Pulmonary Fibrosis by Cortisone

IN a preliminary report, R. M. Friedenberg and S. Rubenfeld (*American Journal of Rœntgenology*, August 1954, **72**, 271) record their findings in nine patients with histologically proven carcinoma of the lung, who were treated with intensive deep x-ray therapy, followed by cortisone. Cortisone was given orally in daily

doses of 100 mg., starting one week after deep x-ray therapy had been instituted, and continued for one to two weeks after it was stopped. In none of them has radiological evidence of pulmonary fibrosis appeared: six of them have been followed for over three months. It is also reported that in some cases the administration of cortisone was accompanied by a decrease in pain and dyspnœa, and an increase in weight. None of the patients developed radiation sickness. In another patient who had a severe reaction to deep x-ray therapy, including massive fibro-atelectasis, relief followed the administration of cortisone and has been maintained for four months after the withdrawal of cortisone. It is pointed out that 'precise evaluation of a study of this nature is impossible' without further evidence, but the findings suggest that cortisone may be of value in inhibiting pulmonary fibrosis following irradiation'.

A New Test for Phlebothrombosis

THE following simple test is recommended by R. I. Lowenberg (*Journal of the American Medical Association*, August 28, 1954, **155**, 1566) as a useful confirmatory measure in the diagnosis of phlebothrombosis. In patients suspected of having phlebothrombosis the sphygmomanometer cuff is fastened round the calf or thigh and slowly distended (i.e., in 10 to 15 seconds). Normally patients do not register discomfort below a pressure of 180 mm. Hg in the calf or thigh, but in the presence of phlebothrombosis 'the patient will complain bitterly of pain at a level significantly below the normal'. As soon as pain or discomfort is evoked, the cuff is deflated and the test is repeated on the other calf (or thigh). Should there still be any doubt about the patient's level of pain sensitivity, the test can be repeated on the arm, where most patients will tolerate 250 mm. Hg without discomfort. 'A positive sphygmomanometer cuff pain test is recorded when there is a clear-cut patient pain response anywhere from 60 to 150 mm. Hg. This can be repeated for clarification, and the end point should be within 10 mm. Hg of the previous recording'. Another point to be noted is that 'Discomfort is registered always in the segment of extremity covered by the pneumatic cuff. The patient will usually relate to the examiner that the cuff was tighter at the strongly positive location than at the same position on the other leg, although the pressure might have been 100 millimetres less'.

Myxomatosis

LAST autumn, E. J. Moynahan (*Guy's Hospital Gazette*, October 2, 1954, **68**, 391) was asked by the Ministry of Health to see the first alleged human case of myxomatosis in this country. This was a pest control officer who had been engaged in the destruction and disposal of infected rabbits. Soon after he had been engaged in this work he developed conjunctivitis in one eye, which responded quickly to his doctor's treatment. Two days later he developed a bullous eruption on the face, with an associated submental lymphadenitis, which was aggravated, rather than relieved, by penicillin cream. Because of the similarity of the condition to the disease in rabbits, the wife diagnosed myxomatosis and informed the press accordingly. When the patient was seen at Guy's Hospital, he had a few crusted impetiginous lesions on the chin, with a little œdema, and the submental glands were still enlarged. Pulse and temperature were normal, and there was no abnormality in any other system.

Moynahan points out that there have been several reports of human infection, but 'no case diagnosed as such in humans has been subsequently confirmed'. On the other hand, 'it is impossible to say that no human cases of myxomatosis will occur, particularly as the virus seems to be unstable, but it is highly unlikely'. In the differential diagnosis, the conditions that should be borne in mind are: bullous erythema multiforme; Stevens-Johnson's syndrome; atypical cases of chickenpox and smallpox; human foot and mouth disease; bullous dermatitis herpetiformis; early cases of pemphigus, especially when the eyes are involved. He also draws attention to the possibility of localized infection with common pyogenic organisms, e.g., septic wounds in the hands, in persons who have been in contact with myxomatosis-infected rabbits, being mistaken for myxomatosis by the patient and his relatives. 'Such lesions are not uncommon in those who handle animals of all kinds, but when public emotion is raised to a high pitch, as it has been over myxomatosis, the importance of recognizing them for what they are cannot be overstressed'.

A Sign of Achlorhydria

'A BAND of redness half an inch wide on the nose about half to three-quarters of an inch from the tip' is said by Edith E. Anderson (*Medical Journal of Australia*, July 24, 1954, **ii**, 156) to be a sign of achlorhydria in the adolescent. For many years she has had the opportunity of observing several familial cases of achlorhydrosis and she has found that this band is usually present. She comments: 'It does not seem to be often recognized in the late adolescent, judging from the number of people who have been taking antacid mixtures unnecessarily'.

REVIEWS OF BOOKS

Lectures on the Thyroid. By J. H. Means, M.D. Cambridge, Mass.: Harvard University Press; London: Geoffrey Cumberlege, 1954. Pp. ix and 113. Figures 11. Price 24*s*.

For so many years anything written on the thyroid gland by Dr. Means has been read with attention and has commanded such respect that his name alone will make anyone who is interested in the thyroid wish to read this book. They will not be disappointed. It comprises five lectures in which are reviewed the recent work on two scientific subjects, namely, the integrative action of the endocrine system and the thyroid hormone, and three more clinical subjects—the use of hormones, drugs and radiation in the management of thyroid disease, a discussion of the etiology of Graves' disease, and the need for iodine. The vast experience and knowledge of the author have enabled him to handle these subjects and place them in their true perspective, and to these reviews he adds his own ideas about lines of research that are likely to be profitable in the future. His style is clear and simple, and anyone who has read this book will have a pleasant feeling that he is up-to-date with the thyroid gland, if only for a short time.

Hypertension: Humoral and Neurogenic Factors. Edited by G. E. W. Wolstenholme, O.B.E., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S. London: J. & A. Churchill Ltd., 1954. Pp. xiv and 294. Illustrations 73. Price 30*s*.

This book is based on the proceedings of a symposium on hypertension arranged by the Ciba Foundation in London last year, at which papers were read by leading research workers from 14 different countries. Hypertension is discussed not in relation to its epidemiology or clinical aspects but from the point of view of applied physiology, pharmacology, endocrinology and biochemistry. Although it is evident that the fundamental causes of hypertension in man and of experimental hypertension in animals are still obscure, as is the relationship of one to the other, facts are steadily accumulating. Neurogenic hypertension is discussed in relation to its experimental production, its reflex regulation and to drugs which block the sympathetic nervous system centrally, at the autonomic ganglia or peripherally. Humoral factors include renin, angiotonin, serotonin and catechol amines. Some workers still support the theory of a positive pressor factor produced by the kidney which elevates the blood pressure. Most investigators have failed to find any evidence of a pressor substance in chronic hypertension and consider that an extra-renal pressor mechanism exists which is inhibited by the normal kidney and that human essential hypertension and most forms of experimental renal hypertension are due to failure of the kidney to secrete a substance which has the property of preventing hypertension.

The value of this book is for research workers and all who are interested in keeping abreast of what is being done in this field. If there are few agreed conclusions there is much to stimulate thought and provoke ideas for further research and it is from such efforts that the answers will eventually come.

The Foundations of Surgery. By George Perkins, *M.C.*, M.Ch., F.R.C.S. Edinburgh: E. & S. Livingstone Ltd., 1954. Pp. viii and 236. Price 10*s*.

This book is intended to give a student on his first entry into the clinical period some grounding in the principles of surgery. It consists of a number of short chapters, forty-six in all, in which an attempt is made to explain in simple language the basic processes in pathology, the methods of clinical examination, and the various diseases and injuries which the student will meet in his surgical appointments. The task of presenting surgery in simple language is a difficult one, and Professor Perkins has tackled it manfully, but not with outstanding success. The chapters on chronic inflammation, on shock, on burns, on the breast, and on the acute abdomen are sketchy and not entirely up to date, and it cannot be claimed that this will make the student's work any easier when he comes to read a standard textbook. In his preface the author says that the title should have been 'Surgery for Toddlers'. The toddler wants something much more dramatic with plenty of nice pictures.

Practical Fluid Therapy in Pediatrics. By Fontaine S. Hill, M.D. Philadelphia and London: W. B. Saunders Co., 1954. Pp. xx and 275. Price 30*s*.

This is a valiant book which tries, in painstakingly simple language, to explain how to avoid fluid and electrolyte misadventures. The book starts off by defining all the terms in current use and then considers, again in simple language, the physiological principles concerned in the electrolyte composition of the body, abnormalities of the pattern, and the part played

by the kidney in maintaining and restoring the proper balance. The second section of the book is a consideration of the clinical applications of the principles laid down in the first part. There are chapters on the various types of solution for intravenous administration, and more specific diseases, such as diarrhœa, renal disease, infections, burns and pyloric stenosis, are discussed at length; the final section of the book is a short one on technical procedures.

Because of the simple way in which this difficult subject is described, Dr. Hill's book should have a considerable appeal to those who wish to familiarize themselves with the current practice of fluid therapy in infancy and childhood. From the clinician's viewpoint everything he will need to know is included, and if at times an argument is not sustained, but ends with the abrupt and rather irritating 'Gamble says' or 'Darrow says', what these authorities said is more likely to be right than what somebody else has failed to say, and does not detract from the value of the book.

Historical Review of British Obstetrics and Gynæcology. 1800-1950. EDITED BY J. M. MUNRO KERR, LL.D., M.D., F.R.F.P.S., F.R.C.O.G., R. W. JOHNSTONE, C.B.E., LL.D., M.D., F.R.C.S.ED., F.R.C.O.G., and MILES H. PHILLIPS, M.B., F.R.C.S., F.R.C.O.G. Edinburgh: E. & S. Livingstone Ltd., 1954. Pp. viii and 420. Price 30*s*.

THIS history of British midwifery and gynæcology, planned to be published in conjunction with the semi-jubilee celebrations of the Royal College of Obstetricians and Gynæcologists, is written as a sequel to H. R. Spencer's 'History of British Midwifery 1650-1800'. The book opens with a general review of the period, 1800-1950, by R. W. Johnstone and Munro Kerr, with a concluding section by Bethel Solomons on developments in the same period in Ireland. This is followed by a series of chapters on 'special subjects', including the history of antenatal care (F. J. Browne), pregnancy and associated diseases (Dame Louise McIlroy), obstetrical anæsthesia (A. M. Claye), radiography (G. I. Strachan), maternal mortality (Gilliatt), the teaching of midwifery (Eardley Holland), obstetrical societies, obstetrical journals (James Young), and midwife services (Arnold Walker).

This may not be an inspired book but it is a worthy sequel to Spencer's work and will undoubtedly remain the authoritative work on the subject for many years to come. It has the great advantage of being written by experts and is therefore not only authoritative but also written with that first-hand experience of the subject which ensures that the emphasis is always put in the right place. The editors state that 'publication of this volume has been made possible through the cooperation and generosity' of the publishers. Those who compare the price (30*s*.) with prices of books of comparable size will appreciate the practical form which the generosity of E. & S. Livingstone has taken.

Experimental Diabetes and its relation to the Clinical Disease. EDITED BY J. F. DELAFRESNAYE and G. H. SMITH. Oxford: Blackwell Scientific Publications, 1954. Pp. ix and 352. Price 35*s*.

THIS volume will appeal to those with a specialized interest in diabetes. Most of the nineteen papers, which were delivered at a symposium organized by the Council for International Organizations of Medical Sciences, deal with animal experiments. It is apparent from the verbatim reports of discussions which followed each paper that the results obtained, although of much intrinsic interest, were often controversial, and that final conclusions must await the outcome of further investigations. In these circumstances it would be impossible to apply much of this experimental work in any practical way to the clinical disease, and the second part of the title of this book may prove somewhat misleading. Among the subjects discussed are the morphology of the islets of Langerhans, the hyperglycæmic-glycogenolytic factor (glucagon) of the α-cells, the diabetogenic action of growth hormone and its relation to insulin, the adrenal cortex and carbohydrate metabolism, and the mechanism of alloxan diabetes. On the clinical side, there are papers on heredity in diabetes, clinical types of the disease, and the diabetogenic action of pregnancy.

The publication of these proceedings is welcome, but it is unfortunate that they should not appear until 18 months after the papers were delivered.

Having a Baby. BY J. F. ROBINSON, M.B., CH.B. Edinburgh: E. & S. Livingstone Ltd., 1954. Pp. viii and 92. Figures 23. Price 6*s*. 6*d*.

THIS little book is written in simple style with suitable diagrams for the use of antenatal patients. The chapters on antenatal care and the hygiene of pregnancy are especially commendable. The chapters and sub-headings are spaced out well for the non-medical reader. It is perhaps a pity that the valuable chapters on 'contraception' and 'sterility' appear so early in a book with the title *Having a Baby*. It might perhaps be more fitting to have these chapters as an appendix in the next edition. On the strictly medical side there are three criticisms. First, the suggestion that the vulva should be

washed with soap and water thrice daily is open to criticism, perhaps mainly by the dermatologists. Secondly, a dozen lines on the very important subject 'Care of the Nipples' seems to be inadequate. Thirdly, the author states 'Some people have very short periods and lose hardly any blood at all while others may have a heavy loss of blood for 7-8 days'. Most gynæcologists would regard a heavy loss of 8 days as menorrhagia requiring investigation. The book is attractively produced and is suitable for the use of patients attending antenatal clinics.

NEW EDITIONS

Practical Obstetrics, by Bruce T. Mayes, M.V.O., M.B., B.S., F.R.C.S.ED., F.R.C.O.G., second edition (Angus and Robertson Ltd., 87*s.* 6*d.*).—The appearance of a second and enlarged edition of this book speaks for its usefulness and popularity. Professor Mayes has a great reputation as a clinical teacher of obstetrics. His easy style of writing brings him to the delivery room or one's consulting room to be at hand when one is considering what to do and how to do it in most of the debatable conditions in obstetrical practice. The enlargement of the book is welcome as it has enabled him to cover some important topics previously omitted. This book can be bought with advantage by anyone practising midwifery. What is said by Professor Mayes comes from experience and, though never afraid to express his opinion, he is not dogmatic. Moreover, he believes in profiting from mistakes as well as from successes.

Since the war the Commonwealth countries have been producing some notable medical books. This one is from Australia, and the author and his publishers are to be congratulated upon the work and its standard of production.

May & Worth's Manual of Diseases of the Eye, revised by T. Keith Lyle, C.B.E., M.A., M.D., M.CHIR., and A. G. Cross, M.A., M.D., F.R.C.S., eleventh edition (Baillière, Tindall & Cox Ltd., 35*s.*).—May & Worth's manual has always been a good book. It is balanced, reliable, less prolix than many of its fellows, eschewing the redundant and more fanciful; and in this latest edition under stimulating new management, it is embellished by several new chapters which reach out through the marches where ophthalmology makes contact with the various domains of general medicine, as well as by many excellent illustrations, and a modicum of new writing in the more 'old-fangled' sections. In size it is between the student's handbook and the comprehensive textbook; and although its preface trusts that it will suit all tastes—from undergraduates to specialists, G.P.s, nurses and 'those who work overseas'—it provides a fair coverage for the part-time ophthalmologist or the more casual consultant.

The Anatomy of the Bronchial Tree, by R. C. Brock, M.S., F.R.C.S., F.A.C.S., second edition (Oxford University Press; London: Geoffrey Cumberlege, 45*s.*).—Sir Russell Brock's classic monograph on the anatomy of the bronchial tree has now been accepted as the standard work of reference on this hitherto neglected subject, of such vital importance to clinician, radiologist, pathologist, and physiotherapist. The second edition contains at least one important new chapter, on the standard international nomenclature introduced in 1949 to eliminate the confusion in terminology then in existence. An appendix describing the technique of preparing bronchial casts will be of great assistance to others working in this and allied fields of anatomical research.

The somewhat unusual experiment of illustrating a treatise on anatomy by frequent reference to pathology, in this instance the pathology of lung abscess, has proved fully justified; the text has been enlivened, the clinician's interest stimulated and held, and the relationship between anatomy and pathology reaffirmed at a time when the importance of mechanical factors in the etiology of infection and inflammation has been overshadowed by preoccupation with the immunological problems of virulence and resistance.

Oral and Dental Diseases, by Hubert H. Stones, M.D., M.D.S., F.D.S.R.C.S. (E. & S. Livingstone Ltd., £5).—The publication of a third edition of this book within a period of six years is some indication of the popularity it has achieved. It is now well established as the standard textbook for dental students, both for undergraduates and for postgraduates reading for higher degrees. The present edition retains the previous form of presentation. The few modifications made by the author take account of the advances that have been made in dental science since the last edition in 1951. The chapter on 'Diseases of the nervous system and muscles' has been rewritten with the addition of several further types of neuralgias. A medical practitioner will find it an excellent book to refer to when confronted by oral conditions of which he may have had little experience; it is an easy book to read but holds the attention.

The contents of the December issue, which will contain a symposium on 'Upper Respiratory Infections', will be found on page lxxxvi at the end of the advertisement section.

Notes and Preparations, see page 633
Fifty Years Ago, see page 639

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References: *Schweiz. med. Wschr.*, 1942, **72**, 1350.
Rev. méd. Suisse Rom., 1947, **67**, 112.
Schweiz. Arch. Neurol. Psychiat., 1948, **62**, 128.
Schweiz. med. Wschr., 1948, **78**, 1125.
Thesis, Bordeaux, 1952.

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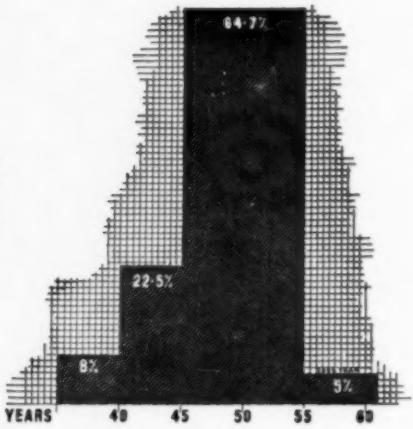

Graph showing percentages of average age of onset of menopause, drawn from figures compiled by the Council of Medical Women's Federation in England.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

'ACHROMYCIN' brand of tetracycline is a derivative of 'aureomycin' and is active against gram-positive and gram-negative cocci, gram-negative bacilli, protozoa and some viruses and rickettsia. The recommended basic adult dosage is 1 gramme daily in divided doses. At present it is only available through National Health Service hospitals and regional distribution centres. Supplied as: 50-mg. (vials of 25 and 100) and 250-mg. (vials of 16, bottles of 100) capsules; vials of 250 mg. and 500 mg. for intravenous administration; and 'spersoids' dispersible powder (jars of 36 g. and 75 g.; each teaspoonful contains 50 mg. of 'achromycin'). (Lederle Laboratories Division, Cyanamid Products Ltd., Bush House, Aldwych, London, W.C.2.)

'CALCIUM DISODIUM VERSENATE' intravenous solution (Riker) is the calcium chelate of ethylenediamine tetra-acetic acid and is intended for the treatment of acute and chronic lead poisoning and lead encephalopathy. 'Marked symptomatic improvement' has been reported also in cases of mercury poisoning. In addition, it is claimed to 'show great promise as a method of removing products of nuclear fission and other radioactive substances, such as radium, plutonium and yttrium'. Issued in boxes of six 5-ml. ampoules. (Riker Laboratories Ltd., Morley Street, Loughborough, Leicestershire.)

'IMFERON' is a 'neutral, isotonic solution' for the treatment of iron-deficiency anæmias. It is suitable for either intravenous or intramuscular administration, and each ml. contains 50 mg. of elemental iron. It is 'stable in the presence of protein and is free from iron ions'. Available in 2-ml. ampoules in boxes of 10 and 100 and in 5-ml. ampoules in boxes of 5 and 50. (Benger Laboratories Ltd., Holmes Chapel, Cheshire.)

'MEPHYTON' (Merck & Co. Inc.) is an emulsion for intravenous injection which 'promptly reverses the prothrombin deficiency induced by coumarin-like compounds'. Its action 'is detectable within minutes and, where hæmorrhage has occurred, bleeding is usually terminated within three hours'. It is also of use, in conjunction with anticoagulant therapy, in maintaining desired prothrombin levels. It contains vitamin K_1, 5%; lecithin, 1%; and distilled water to 100%, and is issued in boxes of six 1-ml. ampoules. (Distributed by Sharp & Dohme Ltd., Hoddesdon, Herts.)

'POLYFAX' is an antibacterial ointment containing bacitracin, which is effective against gram-positive organisms, and 'aerosporin' brand polymixin B sulphate, which is effective against gram-negative bacteria, especially *Ps. pyocyanea*. Issued in 20-g. tubes, and in 4-g. tubes with special nozzle for ophthalmic use. (Burroughs Wellcome & Co., 183-193 Euston Road, London, N.W.1.)

'SULFOMYL' (*p*-sulphonamidobenzylamine propionate) is 'a new sulphonamide for ophthalmic use' and is said to be more effective than soluble sulphacetamide against common infections of the eye, and to be less irritant to the conjunctiva. Available as a 5% solution, in dropper bottles of ½ fluid ounce, and as a 2.5% ointment in tubes of 4 g. (Bayer Products Ltd., Africa House, Kingsway, London, W.C.2.)

'THERMOTABS' each contain 7 grains (420 mg.) of sodium chloride, ½ grain (30 mg.) of potassium chloride, 3/10 grain (18 mg.) of calcium carbonate and 3 grains (200 mg.) of dextrose, and are intended to minimize fatigue and prevent heat prostration 'in those whose work or play results in excessive perspiration'. Supplied in bottles of 1000 tablets. (Sharp & Dohme Ltd., Hoddesdon, Herts.)

NEW APPARATUS

'SURQUAL' minor sterilizer (size 7½ in. x 3½ in. x 2 in.) has been introduced for the sterilization of small instruments, hypodermic syringes and needles, and the like. It is electrically heated and is fitted with an automatic cut-out device. A similar model is available for use with a spirit lamp. (Surgical Equipment Supplies Ltd., Westfields Road, Acton, London, W.3.)

COLLEGE OF GENERAL PRACTITIONERS

THE first *James Mackenzie Lecture* of the College will be given by the President, Dr. W. N. Pickles, at 11.30 a.m. on Saturday, November 20, in the Great Hall, B.M.A. House, Tavistock Square, London, W.C.1. The title of the lecture will be 'Epidemiology in Country Practice'. Visitors will be welcome.

The second *Annual General Meeting* of the College will be held in the Great Hall, on the same day, at 2 p.m.

PRIZE ESSAY COMPETITION

THE *Katherine Bishop Harman Prize*, value £75, was founded for 'the encouragement of study and research directed to the diminution and

CONTINUED ON PAGE 634

avoidance of risks to health and life that are apt to arise in pregnancy and child-bearing', and the Council of the British Medical Association announces that it is prepared to consider an award of this prize in the year 1955, for the best essay submitted in open competition. Any registered medical practitioner in the British Commonwealth and Empire is eligible to compete, and full details may be obtained from The Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1. Essays must be forwarded not later than December 31, 1954.

CHRISTMAS GIFTS FUND APPEAL

LORD WEBB-JOHNSON, President of the Royal Medical Benevolent Fund, writes: 'To receive a gift at Christmas time brings joy to everyone, but particularly to those who are lonely or in need. To none is a gift more welcome than to those who have fallen on hard times. . . . Beneficiaries include colleagues who have met with misfortune, and also widows and spinster daughters who are often in desperate need. I ask readers to give generously and to bear in mind that many of the widows are young women with children, the breadwinner having been plucked away before he was able to make provision for them. The Fund helps them by regular grants in aid, but an additional gift at Christmas sets their hearts aglow'. Contributions should be sent to the Secretary of the Royal Medical Benevolent Fund, 1 Balliol House, Manor Fields, Putney, London, S.W.15, and marked 'Christmas gifts'.

NAPT CHRISTMAS SEALS

THIS year marks the fiftieth anniversary of the issue of the first Christmas seal, in Denmark. Since then the idea has spread all over the world, and in the last twenty-one years these seals have been the main source of income for the NAPT in Great Britain. The 1954 seal is a gay design of holly and candles in bright blues, green and gold and bears as usual the double-barred red cross—the international symbol of the fight against tuberculosis. These seals are a colourful decoration for letters and parcels and cost only 4*s.* for a sheet of 100. There are Christmas cards to match at 8*s.* a dozen, or in black and white with a coach and horses design at 4*s.* a dozen. Supplies may be obtained from the Duchess of Portland, Chairman, NAPT, Tavistock House North, London, W.C.1.

NATIONAL SPASTICS SOCIETY APPEAL

DURING the next five years the Society proposes to allocate £45,000 to research work and is therefore launching a special appeal for funds during the next six months. It is hoped to raise a large sum by the sale of Christmas seals which have been designed by well-known artists. Supplies of seals, at 1*d.* each or in sheets of 120 for 10*s.*, and also sets of six Christmas cards (with envelopes and seals) in four designs, at 2*s.*, 2*s.* 6*d.*, 3*s.*, and 4*s.*, may be obtained from The National Spastics Society, 44 Stratford Road, London, W.8.

THE ROYAL MARSDEN HOSPITAL

THE Minister of Health has promulgated an Order, whereby from October 1, 1954, the name of the Royal Cancer Hospital (Free), London, S.W.3, has been changed to the Royal Marsden Hospital.

MARRIAGE, DIVORCE, AND FERTILITY

IN the latest section of his Statistical Review for 1952, the Registrar General reports that in that year there were 349,308 marriages, representing a marriage rate of 15.8 persons marrying per 1000 population. The most popular month was March (69,832 marriages) and the least popular was January (13,968). The most popular age of marriage was 23 for men and 21 for women. There was a further rise in the proportion of civil ceremonies (i.e. in Register Offices), compared with church ceremonies: the proportion per 1000 marriages was 306 for civil ceremonies, 496 for the Church of England and the Church of Wales, and 94 for the Roman Catholic Church. The comparable figures for 1934 were 284, 535, and 65.

The number of new divorce petitions filed fell from 38,382 in 1951 to 34,567, the most frequent causes being desertion (15,870 cases) and adultery (13,010 cases). In 10,995 cases there were no children of the marriage; in 296 cases there were seven or more children. During the year there were 8,590 confinements resulting in multiple births, of which 64 were of triplets and one of quadruplets. Examination of the 1952 death records showed that 17.7% of married women died without having borne children. During the year, 13,296 children were adopted. In 59% of the adoptions of legitimate children, at least one of the adopters was related to the child; the corresponding proportion for illegitimate children was 34%.

PEPPERMINT AND DENTAL CARIES

IN a recent issue of the *British Dental Journal* (1954, **97**, 162) a correspondent raises the question of whether there is 'a connexion be-

CONTINUED ON PAGE 636

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tween the sucking of peppermints and the extremely rapid type of caries sometimes seen in adult patients'. He states that he himself is 'convinced that there is, having observed it for some years in regular patients, hitherto fairly free from caries, and entirely free from cervical caries, who, wishing to give up smoking, have taken to eating peppermint sweets—especially one particular brand'. 'The resultant cervical caries', he reports, 'even in a few months, can be alarming. Just as quickly, by stopping the use of peppermint, the mouth seems to resume its original caries immunity, although the consumption of other forms of confectionery is not limited'.

BATS AND RABIES

It was only some twenty years ago that definite evidence was obtained that hæmatophagous bats could transmit rabies to cattle and man. Previously, the traditional view had been accepted that the principal role in the transmission of the disease was played by the dog and the wild Carnivora. As hæmatophagous bats are only found in Latin America, the problem is a relatively confined one, but the extent of the problem can be judged from the fact that in Mexico, for instance, between 1931 and 1943 there were 10,000 cases in cattle each year, and in the affected herds from 20% to 50% of the animals were lost. These, and many other facts, are summarized by Victor Carneiro of Brazil in the current issue of the *Bulletin of the World Health Organization* (1954, **10**, 775). Although the first serious outbreak of bat-transmitted rabies was in 1908, it was not until after the outbreak in Trinidad in 1925, when 80 cases of bat-transmitted rabies in man were reported, that definite proof was obtained that the vampire bat could transmit the disease. An interesting feature of bat-transmitted rabies is that the infected individual, or animal, does not show the classical excitability and fury, but that paralysis predominates. It is not surprising therefore that in the Trinidad outbreak the preliminary diagnosis was poliomyelitis.

'DEATH IN THE ICEBOX'

In an editorial with this arresting title, the *New England Journal of Medicine* (1954, **251**, 79) draws attention to the latest hazard to the young of America—the discarded refrigerator. 'The very nature of its function—to provide a hermetically sealed and insulated cabinet—and the ingenious absolutism of its one-way latch make it as perfect a deathtrap as if it had been designed for the purpose'. Apparently the problem has reached such a stage that laws are being passed 'requiring the removal of latches or doors from unused or discarded refrigerators before they are left where the adventurous young can enter them'. It is reported that in the six years, 1948-53, 1 to 5 children in each of nearly 50 incidents were trapped in ancient but airtight refrigerators. 'Fifty-nine boys and 20 girls, ranging in age from two to twelve years, have thus had their lives literally snuffed out from lack of oxygen'. The number of fatalities in 1953 was double that in 1952, with an increase in the number of deaths per incident: in one case, five children from a single family were the victims. That the problem has serious potentialities is suggested by the fact that it is estimated that there are more than 50,000,000 refrigerators and other airtight cabinets in use at the present time, and that these are being replaced at a rate of between 2,000,000 and 3,000,000 a year.

'MODERN HEALTH'

Under this generic title a series of books intended to provide the layman with 'precise authoritative information' on matters of health is being published under the general editorship of Lord Horder. The first four titles, which have now been published, are: 'Heart Disease' by Dr. Geoffrey Bourne; 'Rheumatism' by Dr. W. S. C. Copeman and Dr. R. M. Mason; 'Varicose Veins' by Dr. Rowden Foote; and 'Epilepsy' by Dr. Letitia Fairfield. (Gerald Duckworth & Co. Ltd., price 8*s*. 6*d*.)

PUBLICATIONS

Notes on Infant Feeding, by Stanley Graham, M.D., F.R.C.P.ED., F.R.F.P.S.G., and Robert A. Shanks, M.D., M.R.C.P., F.R.F.P.S.G., in its fourth edition, epitomizes present teaching, the authors having admirably fulfilled their purpose of compiling notes for the use of medical students that will also be found of value to the family doctor. Here the scientific basis of infant feeding and the practical applications are so clearly and concisely stated that the reader needs no complicated tables or elaborate formulæ to prescribe feeds for individual infants. There is a useful appendix of normal anthropometric values. Teaching to be concise must be dogmatic—individual pædiatricians might disagree with the authors on minor points but the booklet as a whole is admirably balanced and can be warmly recommended. Readers of this edition are likely to use it so often that they would be willing to pay more for a cloth-bound fifth edition. (E. & S. Livingstone Ltd., price 5*s*.)

Your Heart and You, by William A. Brams, M.D., has as its aim 'to incorporate information about coronary thrombosis which will be of interest to the patient, his friends and relatives'. It is designed to act as a supplement to what the

CONTINUED ON PAGE 638

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patient has been told by his own doctor. As one would expect from a cardiologist of Dr. Bram's standing, it is essentially sound and, in the preparation of this English edition, care has been taken to incorporate information on problems of insurance, compensation and rehabilitation as they affect British readers. (Hutchinson, price 9*s*. 6*d*.)

The Separation of Protein Fractions from Human Plasma with Ether (Medical Research Council Special Report Series No. 286), by R. A. Kekwick and Margaret E. Mackay, is a carefully documented description of the authors' procedure for using ethyl ether as a fractionating agent for the proteins of blood plasma. The aim of the method is to keep the process as simple as is consistent with the production of materials of adequate purity, yield and concentration for clinical purposes. The report concludes with a review of the clinical applications of plasma fractions. (H.M. Stationery Office, price 6*s*.)

Expert Committee on Venereal Infections and Treponematoses. Subcommittee on Serology and Laboratory Aspects, W.H.O. Technical Report Series No. 79, deals with important developments, including the production, control and use of cardiolipin antigens; the use of freeze-dried sera; the stability of blood and serum samples transmitted by post; and the results obtained with the *Treponema pallidum* immobilization test. (H.M. Stationery Office, price 3*s*. 6*d*.)

A Toast to Lady Mary, by Doris Leslie, is a novel based upon the life of Lady Mary Wortley Montagu, whose medical claim to fame is that she introduced smallpox vaccination into this country. For those who like their history dished up in the form of fiction, this somewhat gauche picture of one of the leading characters of 17th century society will undoubtedly have an appeal. (Hutchinson, price 12*s*. 6*d*.)

Fourth International Conference on Planned Parenthood.—The report of the Proceedings of this conference, which was held in Stockholm in August 1953, have now been published. (International Planned Parenthood Federation, 69 Eccleston Square, London, S.W.1, price 10*s*. 6*d*.)

Einrichtung und Arbeitsweise einer Blutbank, by Dr. W. Heim and Prof. P. Dahr, gives a detailed and clear account of current blood-bank procedures, and the organization of a hospital blood transfusion service. The book is of convenient size, well printed and illustrated, and references to facilitate additional reading are included for each section. It can be recommended to all concerned with the provision of a hospital transfusion service as a useful and practical handbook. The advice contained in its pages is sound and sufficiently up to date to include, for example, an account of a method of storage of red cells in glycerol-citrate at sub-zero temperatures. (Georg Thieme, price DM 33.)

Blackwell Scientific Publications 1954 Catalogue is now available. It is claimed to be 'the longest and most comprehensive list of medical monographs in the English language'. Copies can be obtained on application. (24-25 Broad Street, Oxford.)

OFFICIAL NOTICES

Aureomycin and Terramycin.—The Ministry of Health announces that as from November 1, 1954, aureomycin and terramycin will be freely prescribable within and outside the National Health Service.

Tetracycline.—The Ministry of Health has arranged for tetracycline to be made available to hospitals in the National Health Service from October 15, 1954, It has also been made available to general practitioners through the regional distribution centres from which aureomycin and terramycin have hitherto been obtained, and for the same conditions as were specified for these two antibiotics. The Ministry has been 'advised by the Medical Research Council that tetracycline is suitable for treatment of the same conditions as aureomycin and terramycin and its toxicity is also similar so that the same precautions should be observed in its employment'.

General Practitioners' Surgery and Waiting Room Accommodation.—In a letter to the clerks of executive councils the Ministry of Health states that 'the Minister has been in consultation with representatives of the medical profession and is pleased to be able to say that the General Medical Services Committee of the British Medical Association is about to make a further effort, through Local Medical Committees, to obtain a comprehensive picture of the general standard of doctors' accommodation and to prevail upon doctors to carry out further improvements wherever necessary. Local Medical Committees will, the Minister understands, be undertaking the detailed inspection of doctors' accommodation and have been asked to keep the Council informed of their arrangements. In so far as they need the help of Executive Councils, the Minister feels sure that this will always be given, e.g., in authorizing where necessary the visits'.

THE PRACTITIONER: 50 Years Ago. See page 639

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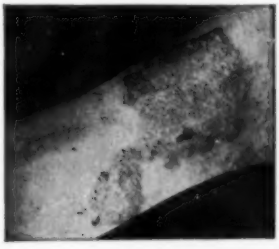

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THE PRACTITIONER
Fifty Years Ago

'No lady is ever a gentleman.'—J. B. Cabell: *Something about Eve* (1927).

NOVEMBER 1904

'THERE can be no doubt,' comments the Editor fifty years ago, 'that the women of the upper classes in the present day take much more physical exercise and use their muscles more than those of bygone generations; and this fact is often pointed to as a hopeful feature, as tending to the production of a more vigorous race. Some gynæcologists and obstetricians hold, we believe, that advanced muscular development is unfavourable rather than beneficial to women in the act of parturition, and tends to make labour more difficult and hazardous than in less muscular individuals. . . . A difficult labour cannot but have an ill effect upon the child, increasing the risks not only of death in the process but also of various forms of injury; so that it seems important to know for certain what are the real facts of the case. Probably the middle course is here as elsewhere the best. A moderate amount of exercise tends to promote health in all directions, while undue indulgence in athletics is bad for both man and woman. But if the dangers of athleticism are as above suggested in the case of women, then we think that those members of our profession who are specially conversant with these matters should point out the risks in no uncertain language, so that parents of girls may at least know the real effects of that physical exercise upon which the spirit of the age seems to set so great a store'.

After confessing that 'the study of medical history does not flourish luxuriantly in this country—It is not a paying branch of investigation, and it needs a considerable expenditure of time and trouble', 'Notes by the Way' welcome 'the more cordially any attempts to encourage the study among us. The recent foundation of the FitzPatrick Lectures before the Royal College of Physicians marks a noteworthy step in the right direction. . . . The first lecturer under this trust was Dr. Payne, than whom no more suitable exponent of the lore of the past could have been chosen. He took for his subject "English Medicine in Anglo-Saxon Times" '.

The opening article is an address 'On Tactile Sensation', delivered before the Wimbledon and District Medical Society by Sir Victor Horsley, F.R.C.S., F.R.S., Surgeon to University College Hospital, and to the National Hospital for Paralysed and Epileptic. It contains a number of interesting references to Galen: 'I am fond of referring to Galen, because it is perfectly astonishing what an amount of accurate neurological knowledge Galen acquired by his experiments on the lower animals and demonstrated to his pupils in Rome. His descriptions of the arrangements of the channels and centres in the spinal cord were forgotten until about twenty years ago, when Professor Ferrier demonstrated that the whole spinal cord was built up of definite centres for definite groups of muscles. Galen had not only demonstrated them scientifically, but had actually used the knowledge for purposes of clinical diagnosis'. One of the plates illustrating this article is taken from 'Dr. Head's well-known work on the distribution of the various spinal roots to the different areas of the skin, trunk, and limbs. It is exactly the distribution which Galen foreshadowed'.

J. D. Rolleston, M.D., F.R.C.P. (1873-1946)

J. D. Rolleston, M.A., M.D., Assistant Medical Officer at the Grove Fever Hospital

of the Metropolitan Asylums Board, contributes the first instalment of 'Clinical Observations on Diphtheritic Paralysis'—a dissertation for the degree of Doctor of Medicine in the University of Oxford—which, like so many articles from his pen, has a long and learned historical introduction. John Davy Rolleston, son of George Rolleston, Linacre professor of anatomy and physiology at Oxford, was born in 1873, studied at Oxford and at Charing Cross Hospital, and graduated M.D. in 1904. Specializing in the acute infectious diseases, he served in three of the Metropolitan Asylum Board's hospitals, culminating in the appointment of medical superintendent of the Western Fever Hospital, Fulham, in 1926. A cultured physician, an erudite medical historian, an able editor, and a devotee of Voltaire, he was handicapped by the overshadowing reputation of his 'illustrious brother', Sir Humphry Rolleston. He died in London on March 13, 1946.

H. S. Clogg, M.S., F.R.C.S., Assistant Surgeon to Charing Cross Hospital, and Surgeon to In-Patients, Evelina Hospital for Sick Children, writes on 'Congenital Hypertrophic Stenosis of the Pylorus', which he attributes to a 'disturbance of the nervous coordination of the stomach, producing spasm of the sphincter muscle', and for the cure of which he favours gastroenterostomy. Herbert Sherwell Clogg (1874-1932) was a surgeon 'with a perfect pair of hands and a calm demeanour which was never ruffled. He seldom spoke at meetings, but when he did so his observations were astute and practical' (*Lives of the Fellows of the Royal College of Surgeons of England*).

P. Lockhart Mummery, F.R.C.S., Assistant Surgeon to St. Mark's Hospital for Diseases of the Rectum, discusses 'The Present Position of the Treatment for Carcinoma of the Rectum'; William Milligan, M.D., Hon. Surgeon to the Manchester Ear Hospital, reviews recent work in otology; and Thomas J. Horder, M.D., M.R.C.P., Medical Registrar and Demonstrator of Morbid Anatomy at St. Bartholomew's Hospital, presents a review of recent literature on diseases of the kidneys.

Only three books are reviewed this month: vol. V of 'A Manual of Medicine', edited by W. H. Allchin of the Westminster Hospital (687 pages for 10s.); 'Practical Pharmacy and Prescribing for Students of Medicine', by James Calvert of St. Bartholomew's Hospital ('the lack of an index is a serious drawback'); and the first volume of the 14th series of 'International Clinics'. Edited by A. O. J. Kelly.

Adrenaline was first isolated in the crystalline state in 1901 by Jōkichi Takamine, the centenary of whose birth occurs on November 3 this year. One of the first graduates in chemistry of the Imperial University of Japan, Takamine was associated with Parke, Davis and Co. in the United States. 'Novelties and Notices' refer to an 'Adrenalin Inhalant' and an 'Adrenalin Ointment' (Parke, Davis and Co.)

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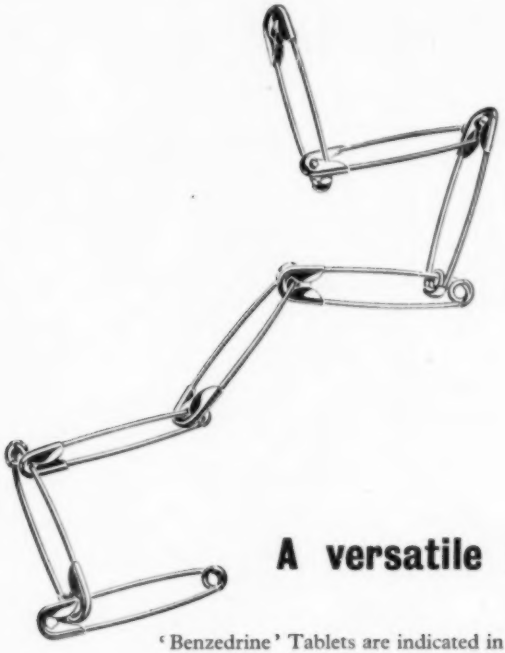

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Physician, Children's Department, and Director, Department of Child Health, Guy's Hospital; Physician, The Hospital for Sick Children, Great Ormond Street

CHRONIC NASAL CATARRH
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Surgeon, Ear, Nose and Throat Department, United Birmingham Hospitals

ACUTE TONSILLITIS
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Assistant Ear, Nose and Throat Surgeon, Royal Infirmary and Royal Hospital for Sick Children, Aberdeen

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Surgeon, Ear, Nose and Throat Department, St. Thomas's Hospital; Surgeon-in-charge, Ear, Nose and Throat Department, Royal Marsden Hospital

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CURRENT THERAPEUTICS LXXXIV.—NALORPHINE
By Andrew Wilson, M.D., F.R.F.P.S.
Professor of Pharmacology, University of Liverpool

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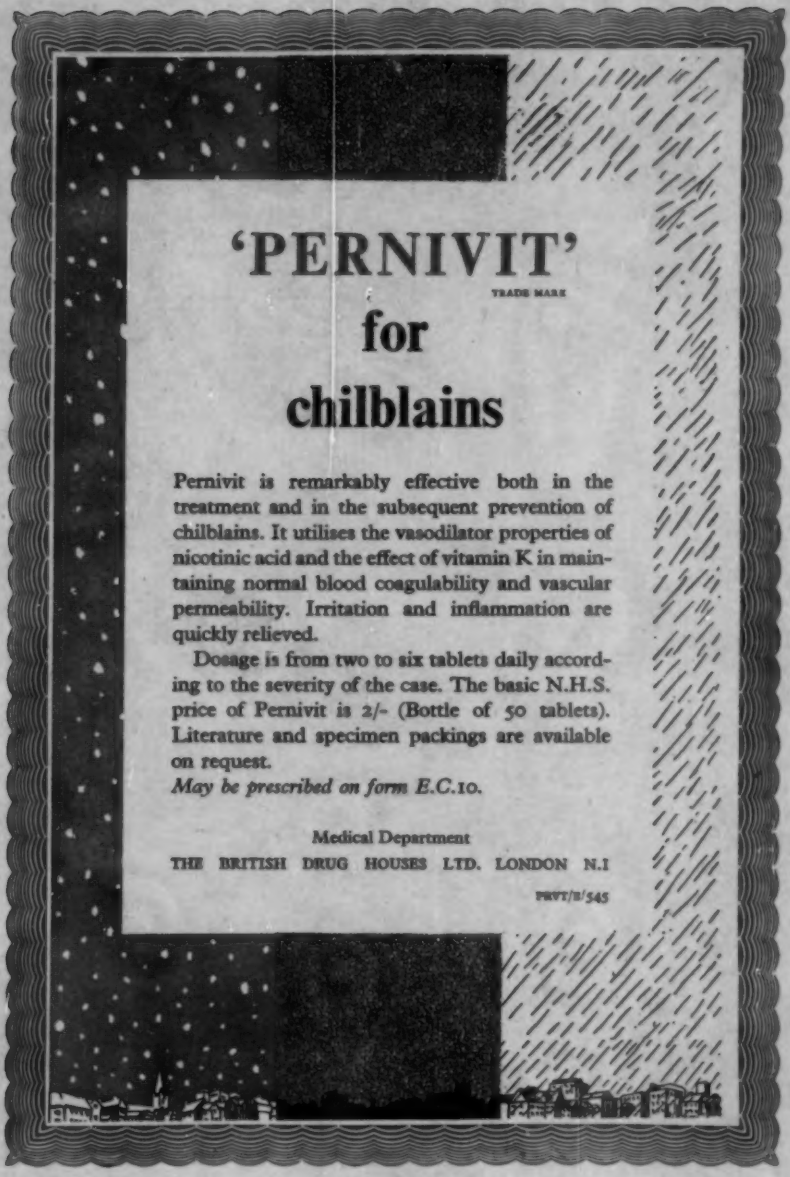

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